Foot and Mouth Disease

Disease Monograph Series – 18

Virus | Aphthovirus | Picornaviridae | Cattle | Buffalo | Sheep | Goats | Pigs

IDRC | Bartay

This monograph forms part of a series of disease monographs commissioned by the International Development Research Centre over the period Nov 2015 to April 2016 to inform funding priorities for the Livestock Vaccine Innovation Fund (LVIF). The LVIF is a seven-and-a-half year, CA$57 million partnership between the Bill & Melinda Gates Foundation, Global Affairs Canada and Canada's International Development Research Centre. It focuses on those animal diseases posing the greatest risk to poor livestock keepers in Sub-Saharan Africa, South and Southeast Asia, targeting transboundary diseases to achieve lasting regional impact.

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Acronyms

AU	African Union
AU-IBAR	African Union Inter-African Bureau for Animal Resources
AU-PANVAC	African Union – Pan African Vaccine Centre
CMI	Cell-mediated Immune Mechanism
CVO	Chief Veterinary Officer
DG	Director General
DIVA	Differentiation of infected from vaccinated animals
DoI	Duration of immunity
DVS	Director Veterinary Services
ELISA	Enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
FMD	Foot and mouth disease
FMDV	Foot and mouth disease virus
GFRA	Global Foot and mouth disease research alliance
IM	Intramuscular
IN	Intranasal
Lpro	Leader protein
NGO	Non-governmental organization

NSPs	Non-structural proteins
OIE	World Animal Health Organization
PCP	Progressive Control Pathway
PCR	Polymerase chain reaction
PIADC	Plum Island Animal Disease Center
QC	Quality control
SC	Subcutaneous
SHF	Small holder farmer
TPP	Target Product Profile
VLP	Virus-like particles
WHO	World Health Organization of the United Nations

Executive Summary

Etiology, epidemiology and impact.

Foot and mouth disease (FMD) is the most contagious disease of mammals and has a great potential for causing severe economic losses in susceptible cloven-hoofed animals.

Foot and mouth disease virus (FMDV) is a member of the genus Aphthovirus in the family Picornaviridae. The FMDV particle consists of the RNA genome surrounded by a protein shell or capsid. The FMDV capsid readily dissociates at mild acidic conditions and at room temperature. There are seven serotypes of FMD virus: O, A, C, Asia-1, SAT-1, SAT-2 and SAT-3. Within these serotypes, more than 65 strains have been recognized. Animals that have been infected by one FMDV do not necessarily have immunity to other strains. Infection provides little or no protection against other serotypes, although there are a few reports of apparent cross-protection in cattle, resulting in milder or asymptomatic infections. SAT strains are highly variable, with many topotypes, and are also less stable than other serotypes.

FMD is typically an acute febrile illness with vesicles on the feet, in and around the mouth, and on the mammary gland. The vesicles usually rupture rapidly, becoming erosions. Pain and discomfort from the lesions leads to clinical signs such as anorexia, excessive salivation, lameness and reluctance to move or rise. In severe cases, the hooves or footpads may be sloughed. Reproductive losses are possible, particularly in sheep and goats. Deaths are uncommon except in young animals, which may die from multifocal myocarditis or starvation. Most adults recover in 2 to 3 weeks, although secondary infections may slow recovery. African buffalo often act as long term reservoir hosts for the SAT serotypes in Africa posing a challenge for FMD control in Southern Africa.

FMDV can be found in all secretions and excretions from acutely infected animals, including expired air, saliva, milk, urine, faeces and semen, in the fluid from FMD-associated vesicles, and in amniotic fluid and aborted foetuses in sheep. Mechanical transmission by fomites and living vectors is important. Airborne transmission can occur under favourable climatic conditions. There are FMD carriers, animals in which either viral nucleic acids or live virus can be found for more than 28 days after infection. Animals can become carriers whether or not they had clinical signs. The epidemiological significance of carrier animals is uncertain and controversial.

Although a disease of low mortality, the global impact of FMD is colossal due to the huge numbers of animals affected. The impact of the disease differs considerable in different parts of the world. It has been estimated that annual impact of FMD in terms of visible production losses and vaccination in endemic regions alone amount to between US$6.5 and 21 billion. In addition, outbreaks in FMD free countries and zones cause losses of >US$1.5 billion a year.

Incidence / Prevalence

FMD is endemic in parts of Asia, Africa and the Middle East. South America has made big progress in its control. While serotypes O and A are widely distributed, SAT viruses occur mainly in Africa (with periodic incursions into the Middle East) and Asia 1 is currently found only in Asia. Many countries are free of FMD, including Indonesia and Madagascar within the countries of interest. Despite the relevance of the disease, not many prevalence studies are available, and more recent studies focus on molecular surveys.

Diagnosis

Diagnosis of FMD is by virus isolation or by the demonstration of FMD viral antigen or nucleic acid in samples of tissue or fluid. Detection of virus-specific antibody can also be used for diagnosis, and antibodies to non-structural proteins (NSPs) can be used as indicators of infection, irrespective of vaccination status. However, in order to use the DIVA (differentiate infected from vaccinated animals) tests, the vaccine should be purified to so they are free of immunogenic contaminating NSPs.

Control

Measures taken to control an outbreak include quarantines and movement restrictions, euthanasia of affected and exposed animals, and cleaning and disinfection of affected premises, equipment and vehicles. Additional actions may include euthanasia of animals at risk. Vaccination may be used to reduce the spread of FMDV or protect specific animals during some outbreaks. The decision to use vaccination is complex, and varies with the scientific, economic, political and societal factors specific to the outbreak. Vaccines are also used in endemic regions to protect animals from illness. FMDV vaccines only protect animals from the serotype(s) contained in the vaccine. Experimentally, interferon has been evaluated to stop the disease while the immunity elicited by vaccination develops.

Import regulations help prevent FMDV from being introduced into free areas. Global FMD control programs have been established by FAO and OIE to reduce virus circulation and the incidence of this disease. The FMD Progression Control Pathway supported under the global program, has been adopted by many countries.

Current vaccines and recent developments

Currently, a number of commercially manufactured vaccines are available of differing strain composition, antigenic content (can be monovalent or polyvalent), adjuvant formulation and cost. All are produced using inactivated antigens. Duration of immunity is 4-6 months. Inactivated FMD vaccines are unable to induce sterile immunity, and viral replication may happen in the epithelial surface of vaccinated animals, resulting in a carrier

state of FMDV. FMD vaccine is a high-cost product since it must be produced within biosecure facilities. Only purified vaccines have DIVA capability, but they are more expensive to produce.

FMD vaccines may be classified as either 'standard' or 'higher' potency vaccines. Standard potency vaccines contain sufficient antigen to ensure that they meet the minimum potency level required. This vaccine is usually suitable for routine vaccination campaigns. To control FMD outbreaks in naïve populations, higher potency vaccines are recommended for their wider spectrum of immunity as well as their rapid onset of protection.

For cattle vaccines, aluminium hydroxide saponin adjuvanted and oil adjuvanted vaccines may be used. Double oil-emulsion vaccines are thought to provide a stronger and longer antibody response than water-in-oil single emulsion vaccines. Vaccines with oil adjuvants are reported to have a better shelf life. The aluminum hydroxide-saponin formulated vaccines are easier to produce. For pigs, double oil emulsions are preferred due to their efficacy. Aluminum hydroxide vaccines are also less potent per microgram of antigen, and produce a shorter duration of immunity. Strain-related differences may affect vaccine manufacture and storage. SAT viruses are less stable than other serotypes. There is one commercial vaccine combined with Haemorrhagic Septicaemia produced in India.

For adequate protection, the vaccine strains must also be well matched with the field strain. The two important determinants are the ability of the vaccine strain to elicit antibodies that will cross-react and protect against the field or outbreak virus in question and the potency of the vaccine. The *in vitro* tests currently used for vaccine matching present some challenges. Adaptation of field viruses to vaccine production requires adaptation of the virus to culture, and the whole process can take 6 months or more.

Recent developments include the conditional licence in the USA of the replication defective hAd5-vectored vaccine developed by USDA, which Merial is now developing. It has many advantages, but concerns include that immune responses to the vector might limit the efficacy of the vaccine, the high dose required and the cost. USDA is working on a new generation of this vaccine, and OVI is working on its use for SAT serotypes. Commercial synthetic peptide vaccines have been in use in Asia for pigs for several years. They do not work in cattle. Communications from the field in Asia indicate that the vaccines produce good antibody titres, but they are not as effective as inactivated vaccines in preventing clinical signs.

Research & potential new vaccine candidates

There is a need for a better FMD vaccine, and vaccines better adapted to the SAT types. There are many research and government organizations working on new or improved FMD vaccines. ARS-USDA and The Pirbright Institute seem to be leading the field and they have many international collaborations. The Global FMD Research Alliance (GFRA) brings together these organizations. There are also private companies working on FMD, such as Harrisvaccines which has in the pipeline a vaccine based on an alphavirus replicon technology. Zoetis is working with USDA on a leaderless inactivated candidate (FMDLL3B3D), and MSD is working on VLP using a baculovirus expression system. Other commercial producers like Jinyu in China, are also working on improving FMD

vaccines. It is important to note research focused on SAT serotypes. OVI and collaborators have been working on chimeric vaccines, with cell culture adaptation phenotypes, as well as SAT and O viruses' stability. These look like important candidates to consider for Africa. Research is focused in aspects such as improving stability, widening the scope of protection, easiness to introduce field strains, matching the field strains, quantification of the antigen content and integrity. Different strategies are being used including cDNA-derived inactivated vaccines, recombinant proteins, empty capsid vaccines, and DNA vaccines. For more details, see Section 8.

Commercial manufacturers of FMD vaccines

There are several FMD vaccine manufactures in Asia in Africa. Some of the African manufacturers need support on purification of the vaccine in order to get DIVA characteristics, but critical to them is technology transfer for QC, vaccine matching and technology that can facilitate the adaptation of field isolates, especially for SAT types. Similar needs are seen in some Asian manufactures. AAHL, Australia has been helping some of the Asian countries, but would like to increase their support to other SEA countries, which due to animal movements, are the source of the outbreaks. PANVAC has also expressed the need to increase QC in African vaccines, and could benefit of a technology transfer such as that being carried out by AAHL. Methodologies such as the avidity ELISA developed by INTA for evaluation of cross-protection would be a great asset for many manufacturers.

Clinical disease overview

Etiology & Epidemiology

Foot and mouth disease (FMD) is the most contagious disease of mammals and has a great potential for causing severe economic losses in susceptible cloven-hoofed animals.

Foot and mouth disease virus (FMDV) is a member of the genus Aphthovirus in the family Picornaviridae. As an RNA virus, FMDV has significant genetic variability. There are seven serotypes: O, A, C, Asia-1, SAT-1, SAT-2 and SAT-3 (Table 1). Within these serotypes, more than 65 strains have been recognized. Older strains have names such as O1 Manisa or A24 Cruzeiro, but the names of recently isolated strains are more standardized and include the date and location of isolation (e.g., O/UK/35/2001). Some serotypes have been divided into topotypes, genetically and geographically distinct units that contain closely related strains of the virus. Asia-1 viruses have sometimes been classified into various "groups" or lineages [1].

Table 1: Ten leading disease losses globally by livestock disease units (LSU) loss

Serotype	Topotypes	Comments
O	1. Middle East-South Asia (ME-SA) 2. Southeast Asia (SEA) 3. Cathay 4. Indonesia-1 5. Indonesia-2 6. East Africa 7. West Africa 8. Europe-South America	Most prevalent worldwide. ME-SA is the dominant topotype, and contains the PanAsia lineage. Called O by Vallee and Carre who initially discovered it, for the department of Oise in France, where it originated [2]

A	Several topotypes. Novel strains emerged and disappeared regularly in Asia and South America.	Antigenically and genetically diverse. Called A for Allemagne (Germany in French) when first discovered by Valle and Carre.
C		Uncommon. Last cases Brazil and Kenya 2004.
Asia-1	Relatively stable	Sometimes classified into "Groups" or lineages.
SAT-1	Highly variable	SAT: South African Territories
SAT-2	Highly variable	
SAT-3	Highly variable	Uncommon in domesticated animals.

Overall, type O is usually the most prevalent and widely distributed serotype. Serotype O currently contains eight topotypes (see Table 1). Middle East- South Asia (ME-SA) is the dominant topotype, and contains the PanAsia lineage of FMDV. This lineage became prominent in India in the 1990s, spread into most of Asia, and has been responsible for a number of recent outbreaks in FMD-free countries throughout the world. In addition to causing the 2001 epizootic in the U.K., the PanAsia lineage affected Taiwan, Japan, South Africa, France, the Netherlands and South Korea in 2000-2002, and caused epizootics in a number of Middle Eastern countries in 2007. Serotype A is antigenically and genetically diverse, and also contains a number of topotypes. Antigenically novel strains of this serotype have emerged and disappeared regularly in Asia and South America. SAT strains are likewise highly variable. Asia-1 viruses have tended to remain relatively stable in their antigenic types, despite the occasional emergence of new strains. However, this serotype has recently caused a number of outbreaks throughout Asia, and appears to have spread rapidly, causing concern. New Asia-1 variants, which are poorly matched with the standard vaccine strain (Asia-1 Shamir) have been recognized during these outbreaks. Some FMDV serotypes are rarely seen. SAT 3 is uncommon in domesticated animals (although it can be found in wildlife in Africa), and the last known cases caused by serotype C occurred in Brazil and Kenya in 2004.

Types O, A, SAT-1, SAT-2 and SAT-3 are the serotypes usually reported from Africa, while serotypes O, A and Asia- 1 occur in Asia. FMD viruses frequently enter the Middle East from both Asia and Africa. Serotypes O, Asia-1 and A are common in this region, and SAT-1 and SAT-2 viruses also make periodic incursions from Africa. In the long term, the SAT viruses seem able to persist only in Africa. Only serotypes O and A are usually detected in South America. Few outbreaks have been reported from this region in recent years. The predominant FMDV topotypes in a region sometimes remain stable for long periods. However, viruses can also spread into new areas, and new strains can develop spontaneously. It may be difficult to predict the behaviour of a field strain of FMDV unless its epidemiology is already known from other epidemics and controlled experiments.

Based on genetic and antigenic analyses, FMDVs throughout the world have been sub-divided into seven regional pools: Eurasia, Eastern Asia, Southern Asia, Eastern Africa, Western Africa, Southern Africa and South America (Figure 1) which seem to maintain distinct groups of viruses. Certain countries share viruses belonging to two different pools, for example, Egypt and Libya. This tendency apparently reflects some degree of ecological isolation, likely reflecting patterns of animal movement and trade or specific wildlife reservoirs (e.g. African buffalo) within a region. Virus circulation and evolution within these regional virus pools result in changing needs for appropriate vaccine selection. For more details on FMD epidemiology in Africa, see Annex 1.

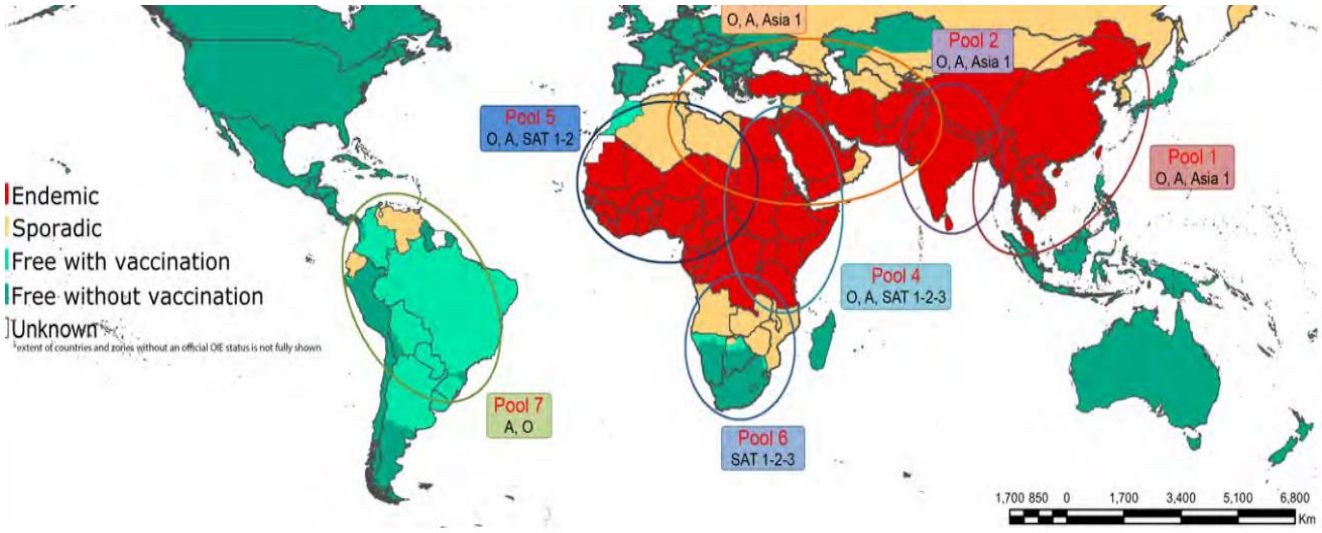
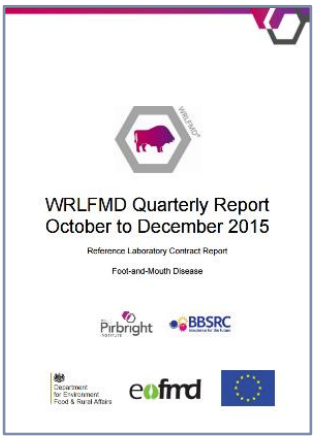


Figure 1: Worldwide distribution of the different FMD serotypes.
Source: Dr King presentation at GFRA Scientific meeting, Hanoi – Vietnam 2015**.**



FAO FMD World Reference laboratory, The Pirbright Institute, produces quarterly reports with a summary of the samples received, virology results, sequence analysis, vaccine matching and vaccine strain recommendations: **http://www.wrlfmd.org/ref_labs/fmd_ref_lab_reports.htm**. As an example, for the latest report (October-December 2015), click on Figure 2.

Figure 2: Worldwide distribution of the different FMD serotypes.
Source: Dr King presentation at GFRA Scientific meeting, Hanoi – Vietnam 2015**.**

FMDV can infect most or all members of the order Artiodactyla (cloven-hooved mammals), as well as a few species in other orders. Livestock susceptible to FMD include cattle, pigs, sheep and goats, as well as Asian water buffalo. Llamas and alpacas can be infected experimentally, but they do not seem to be very susceptible, and natural infections do not appear to be common. Recent studies suggest that Bactrian camels can develop FMD, but dromedary camels have little or no susceptibility to this virus. FMDV is not known to infect horses, mules or donkeys. At least 70 species of wild animals are variably susceptible to FMD. Most are members of the Artiodactyla and include African buffalo, giraffes, wildebeest, blackbuck, waterbuck, wild boar, kudu, impala and tapir. Non-cloven-hooved animals reported to be susceptible to natural and/or experimental infection include European and African hedgehogs, armadillos, kangaroos, nutrias, chinchillas, capybaras, mink, European moles, and voles. Laboratory animal models include guinea pigs, rats and mice, but these species are not important in transmitting FMDV in the field.

Strains of FMDV can vary in their species preferences, clinical presentation, transmission characteristics and possibly their tendency to become established in carriers. While most strains affect all susceptible host species, some have a more restricted host range. Cattle are usually the most important maintenance hosts for FMDV except in Africa, where African buffalo maintain SAT type viruses. There is also evidence that some FMDV isolates might circulate in populations of Asian water buffalo. Some viral strains may primarily be found in pigs, sheep or goats. The pig-adapted serotype O Cathay strain has not infected large ruminants in outbreaks. Some serotype O strains are well-adapted to sheep and goats, although they can also affect cattle. However, it is uncertain whether small ruminants can maintain FMDV for long periods if cattle are absent. African buffalo often act as long term reservoir hosts for the SAT serotypes in Africa; there are reports of FMDV maintained in a herd of African buffalo for at least 24 years. With the exception of African buffalo, there is currently no evidence that wildlife hosts maintain FMDV for more than a few months if domesticated livestock are not infected.

Virus structure

The FMDV particle is roughly spherical in shape and about 25–30 nm in diameter. It consists of the RNA genome surrounded by a protein shell or capsid [2]. The capsid is composed of 60 copies of the capsomers. Each capsomer consists of four structural polypeptides, VP1, VP2, VP3 and VP4. The VP1, VP2 and VP3 are exposed on the surface of the virus while VP4 is located internally. The FMDV capsid (146S particles) readily dissociates at mild acidic conditions and at room temperature into their constituent subunits (12S particles). The protein coat surrounds a single stranded, positive sense RNA genome about 8400 nucleotides (nt) in length. The RNA includes three separate parts i.e. the 5′ untranslated region (5′ UTR), a long coding region and the 3′ untranslated region (3′ UTR) (Figure 3).

The coding region is the major portion of the viral genome. It encodes a large polyprotein which is then cleaved by viral proteases to form four different structural and eleven different non-structural proteins plus a variety of precursors. After translation, initially four primary products are formed, Leader protease (Lpro), P1-2A, P2 and P3. The Lpro is responsible for the inhibition of host cell protein synthesis by inducing the cleavage of the host protein, eIF4G, which is a translation initiation factor that is required for the translation of the capped cellular

mRNAs. As a result, FMDV RNA can freely use the host cell's protein synthesis machinery for its own protein synthesis. The P2 and P3 regions of the polyprotein are processed to the non-structural proteins (NSPs). The P2 region generates the proteins 2B and 2C while the P3 region is cleaved to form the proteins 3A, three distinct copies of VPg (3B1-3), 3Cpro and 3Dpol.

The nucleotide sequences of the VP1 coding region have been used for genetic characterization of FMDV strains because of their significance for virus attachment and entry, protective immunity and serotype specificity.

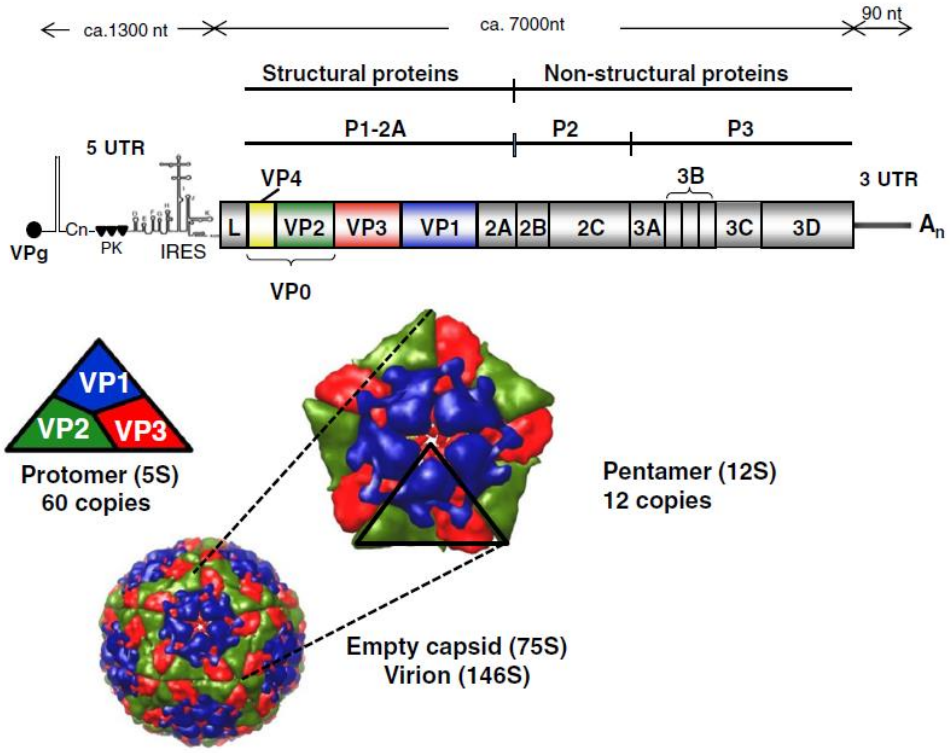


Figure 1 Genome organization of FMDV and the structure of virus. The FMDV genome includes a single large ORF, indicated by the shaded rectangle. The regions within the rectangle indicate the individual proteins. The 5' UTR includes several distinct structural elements including: a poly(C) tract (Cn), 3 or 4 pseudoknots (PK) and the internal ribosome entry site (IRES). The VPg peptide is made in 3 different forms (encoded by the $3B_{1-3}$) and each acts as the primer for RNA synthesis so each RNA genome, when synthesized, is covalently linked to a VPg. The assembly of virus particles from protomeric and pentameric subunits is indicated. Assembled virus particles contain a single copy of the viral RNA and 60 copies of the 4 different capsid proteins (VP1-VP4). Self-assembly of empty capsid particles, lacking the RNA genome, can also occur. The VP4 protein is internal.

Figure 3: Genome organization of the FMDV and the structure of the virus. Source: Jamal and Belsham, 2013 [2]

Serotypes and cross-protection

Animals that have been infected by, or immunized against, one FMDV do not necessarily have immunity to other strains. Conventional inactivated vaccines do not protect animals against other serotypes of FMDV. An infection

also provides little or no protection against other serotypes, although there are a few reports of apparent cross-protection in cattle, resulting in milder or asymptomatic infections. Possible explanations for these cases include immune responses to conserved epitopes recognized by CD8+ T cells and/or to conserved non-structural proteins. Within a serotype, protection between strains varies with their antigenic similarity.

Transmission

FMDV can be found in all secretions and excretions from acutely infected animals, including expired air, saliva, milk, urine, feces and semen, as well as in the fluid from FMD-associated vesicles, and in amniotic fluid and aborted fetuses in sheep. The amount of virus shed by each route can be influenced by the host species and viral strain. Pigs produce large amounts of aerosolized virus, and the presence of large herds of infected swine may increase the risk of airborne spread. Peak virus production usually occurs around the time vesicles rupture and most clinical signs appear. However, some animals can shed FMDV for up to four days before the onset of clinical signs. The virus can enter the body by inhalation, ingestion or through skin abrasions and mucous membranes. Susceptibility to each route of entry can differ between species. Cattle are particularly susceptible to aerosolized virus, while pigs require much higher doses to be infected by this route. Sexual transmission could be a significant route of spread for the SAT type viruses in African buffalo populations. In sheep, FMDV has been shown to cross the placenta and infect the fetus.

Mechanical transmission by fomites and living vectors is important. Airborne transmission can occur under favorable climatic conditions, with some viruses potentially spreading long distances, particularly over water. There is limited information on the survival of FMDV in the environment, but most studies suggest that it remains viable, on average, for three months or less. FMDV is sensitive to pH, and it is inactivated at pH below 6.0 or above 9.0. This virus can persist in meat and other animal products when the pH remains above 6.0, but it is inactivated by acidification of muscles during rigor mortis. Because acidification does not occur to this extent in the bones and glands, FMDV may persist in these tissues. People can act as mechanical vectors for FMDV, by carrying the virus on clothing or skin.

FMDV carriers are defined as animals in which either viral nucleic acids or live virus can be found for more than 28 days after infection. Animals can become carriers whether or not they had clinical signs. The epidemiological significance of livestock FMDV carriers is uncertain and controversial. The only successful experiments were those that involved African buffalo carrying SAT viruses, which transmitted the virus to other buffalo and sporadically to cattle. How long an animal can remain a carrier varies with the species. Most cattle carry FMDV for six months or less, but some animals can remain persistently infected for up to 3.5 years. The virus or its nucleic acids have been found for up to 12 months in sheep (although most seem to be carriers for only 1 to 5 months), up to 4 months in goats, for a year in water buffalo, and up to 8 months in yaks. Individual African buffalo can be carriers for at least five years, and the virus persisted in one herd of African buffalo for at least 24 years. Many outbreaks in Southern and Eastern Africa are linked to buffaloes. Camelids do not seem to become carriers. Pigs are not thought to become carriers.

Clinical Signs

FMD is typically an acute febrile illness with vesicles (blisters) localized on the feet, in and around the mouth, and on the mammary gland. Vesicles occur occasionally at other locations including the vulva, prepuce, or pressure points on the legs and other sites. The vesicles usually rupture rapidly, becoming erosions. Pain and discomfort from the lesions leads to clinical signs such as depression, anorexia, excessive salivation, lameness and reluctance to move or rise. Lesions on the coronary band may cause growth arrest lines on the hoof. In severe cases, the hooves or footpads may be sloughed. Reproductive losses are possible, particularly in sheep and goats. Deaths are uncommon except in young animals, which may die from multifocal myocarditis or starvation. Most adults recover in 2 to 3 weeks, although secondary infections may slow recovery. Possible complications include temporary or permanent decreases in milk production, hoof malformations, chronic lameness or mastitis, weight loss and loss of condition.

Both mouth and foot lesions can occur in water buffalo, but the clinical signs are reported to be milder than in cattle. Pigs, usually develop the most severe lesions on their feet. Mouth lesions are usually small and less apparent than in cattle. FMD tends to be mild in sheep and goats. A significant number of infected animals may be asymptomatic or have lesions only at one site. Common signs in small ruminants are fever and mild to severe lameness of one or more legs. Mouth lesions are often not noticeable and not severe, and generally appear as shallow erosions. Significant numbers of ewes abort in some outbreaks. Young lambs and kids may die due to heart failure (vesicles may be absent) or from emaciation.

Diagnosis

Diagnosis of FMD is by virus isolation or by the demonstration of FMD viral antigen or nucleic acid in samples of tissue or fluid. Detection of virus-specific antibody can also be used for diagnosis, and antibodies to NSPs can be used as indicators of infection, irrespective of vaccination status. However, in order to use the DIVA (differentiate infected from vaccinated animals) tests, the vaccine should be purified to the extent that they should be free of immunogenic contaminating NSPs.

In acutely infected animals, FMDV, its antigens or nucleic acids can be found in a variety of samples including vesicular fluid, epithelial tissue, nasal and oral secretions, esophageal-pharyngeal fluids, blood and milk, and in tissue samples such as myocardium collected at necropsy. Carrier animals can only be identified by collecting esophageal-pharyngeal fluids for virus isolation and/or the detection of nucleic acids.

Serological tests can be used in surveillance, to certify animals for export, to confirm suspected cases during an outbreak, to monitor immunity from vaccination, and in matching vaccines to field strains. Test cutoff values can differ with the purpose of the test. Some serological tests detect antibodies to the viral structural (e.g., capsid) proteins. They include ELISAs and virus neutralization tests, and are serotype specific. Because FMDV vaccines

also induce antibodies to structural proteins, these tests can only be used in unvaccinated animals. Other serological tests (e.g., some ELISAs and the enzyme-linked immuno-electrotransfer blot) detect antibodies to FMDV non-structural proteins (NSPs), which are expressed only during virus replication. NSP tests are not serotype specific, and can be used in both vaccinated and unvaccinated animals. However, they are less sensitive and may not detect cases with limited virus replication, including some vaccinated animals that become infected. Due to such limitations, serological tests that detect antibodies to NSPs are generally used as herd tests.

- OIE recognized tests:

    a) Identification of the agent: virus isolation, enzyme-linked immunosorbent assays (ELISAs), Lateral flow devices, Complement Fixation Test, nucleic acid recognition methods such as reverse transcription polymerase chain reaction (RT-PCR).

    b) Serological tests: Virus neutralization, solid-phase competition ELISA, liquid-phase blocking ELISA.

NSP antibody tests can be measured by different ELISA formats or immunoblotting.

- Differential diagnosis:

Vesicular stomatitis, swine vesicular disease and vesicular exanthema of pigs all produce lesions in cattle or pigs which are clinically indistinguishable from FMD. Conditions which produce erosions or ulceration in the mouth or on the muzzle of livestock, include bovine virus diarrhoea/mucosal disease, bluetongue, malignant catarrhal fever, lumpy skin disease, papular stomatitis, infectious bovine rhinotracheitis and orf (contagious pustular dermatitis). None of these diseases, except bluetongue and occasionally orf, usually produce foot lesions.

Immunity

Humoral immune responses, with the production of neutralizing antibodies, are generally correlated with recovery from infection with FMDV and resistance to reinfection. Cell-mediated immune responses (CMI) have also been reported in FMDV infected animals, although the role of this form of immunity is still under investigation. Mucosal immune responses, with the production of IgA, might also play a role in protection.

Incidence and Prevalence in Selected Countries

Global

Foot and mouth disease is endemic in parts of Asia, Africa, the Middle East and South America. While serotypes O and A are widely distributed, SAT viruses occur mainly in Africa (with periodic incursions into the Middle East) and Asia 1 is currently found only in Asia. See Table 1 and Figure 2.

North and Central America, New Zealand, Australia, Greenland, Iceland and western Europe are free of FMDV. Western Europe was affected by some recent outbreaks (eradication was successful), but FMD has not been reported in North America for more than 60 years. Parts of South America have successfully eliminated FMD with the use of the inactivated vaccine.

FMD is the first disease for which the OIE established an official list of free countries and zones. The OIE has defined a transparent, science-based and impartial procedure for the recognition of FMD disease status of Member Countries and Territories in their entirety or defined zones. Categories for FMD disease status include

FMD free without using vaccination and FMD free with use of vaccination. The latest official status can be seen in Figure 4 below. A detailed list of the countries is included in the following link: **http://www.oie.int/animal-health-in-the-world/official-disease-status/fmd/list-of-fmd-free-members/**

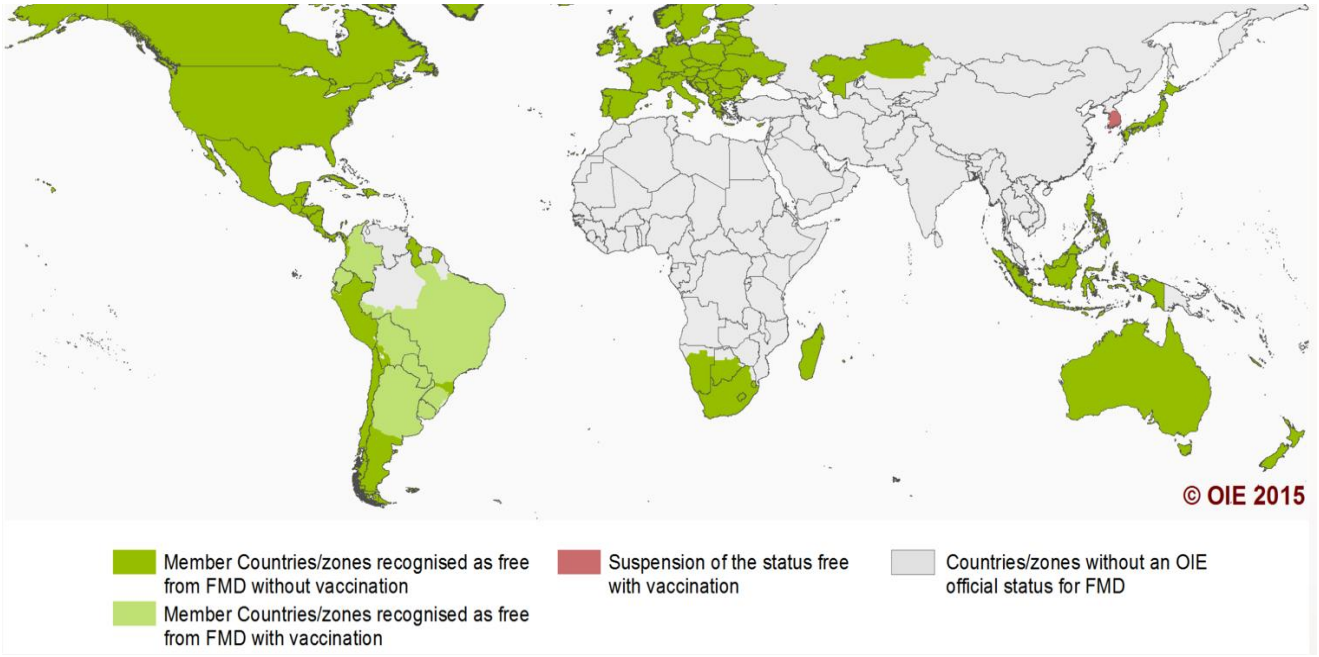


Figure 4: OIE Member Countries' official FMD status map, updated May 2015.
Source: OIE http://www.oie.int/en/animal-health-in-the-world/official-disease-status/fmd/en-fmd-carte/

Incidence FMD data by country

There are two main sources, OIE and AU-IBAR (which includes only Africa), but data are not always similar.

1- Source: OIE.

Data of outbreaks reported to the World Animal Health Organization (OIE) are shown in Tables 2 and 3. Data are not always reliable, as many countries doesn't seem to report, or to be reporting consistently over time.

http://www.oie.int/wahis_2/public/wahid.php/Diseaseinformation/statusdetail

Similar information but presented in a different manner can be seen in Annex 2.

Number of cases reported to the OIE by disease and by country:

- No information, + Present but quantitative data not known, ? Disease suspected

Table 2: Ten leading disease losses globally by livestock disease units (LSU) loss

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Bangladesh	-	-	+	+	+	+	+	+	+	+	-
India	2,270	1,646	1,547	449	902	422	701	879	377	238	-
Indonesia*	0	0	-	0	0	0	0	0	0	-	-
Myanmar	+	>34	17	11	21	10	7	3	9	4	-
Nepal	252	24	>9	>2	204	22	72	41	66	43	36
Vietnam	23	>489	119	>24	218	280	449	34	33	58	-

Table 3: AFRICA – FMD outbreaks notified to OIE from the Asian countries of interest.

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Burkina Faso	66	27	89	89	45	111	161	69	37	193	>28
Ethiopia	24	>8	22	18	>34	67	85	167	63	21	-
Ivory Coast	>4	0	?	4	>6	15	13	5	4	5	11
Kenya	31	42	39	43	62	>61	60	144	42	173	>81
Madagascar*	0	0	0	0	0	0	0	0	0	0	-
Malawi	-	-	-	>4	>1	+	2	0	0	-	-
Mali	22	24	9	11	0	4	3	0	1	6	0
Mozambique	0	0	0	0	0	10	1	0	0	6	-
Rwanda	-	5	>6	>1	>4	>7	?	>23	10	-	-
Senegal	2	46	7	84	42	6	12	15	0	3	5
South Africa	0	2	0	3	4	6	48	5	>13	4	-

Tanzania	34	36	57	27	23	51	14	30	22	18	25
Uganda	5	13	>2	32	>2	4	20	7	6	15	-
Zambia	-	+?	+	9	19	1	0	2	0	0	-

* Madagascar is recognised FMD free by the OIE.

2- Source: AU-IBAR.

The African Union Inter-African Bureau for Animal Resources also has a notification system. Data are published in the Pan African Animal Resources Year Books. (**http://www.au-ibar.org/pan-african-animal-resources-yearbook?showall=&limitstart**=). Similarly to the OIE, many countries do not seem to consistently report the outbreaks.

Note that the number of outbreaks reported often does not match those reported to the OIE.

Table 4: Number of FMD outbreaks per year as reported to AU-IBAR and published in the Pan African Animal Resources YearBook. NS= Not specified

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Burkina Faso	66	20	420	90	40	111	164	69	36	194	
Ethiopia	12		26	56	13	95	87	158	113	7	
Ivory Coast	3			9	6	8	13	10	1	5	
Kenya			140	2	1	NS	28	11	6	48	
Madagascar											
Malawi				1	1		2				
Mali	2			1		4	2			7	
Mozambique						1	5				
Rwanda				6	3	1		1	1		
Senegal		50	7	66	43	6	13	20	7	4	

South Africa		2		12	8	6	69	16	33	5	
Tanzania	22	49	73	0*	NS	NS	11	18	13	14	
Uganda	5	5	4		2		14	3	13	8	
Zambia				0*	1	NS	1		1		

*Cases were reported from outbreaks during the previous years

Regional

Prevalence FMD data by country (from 2000 onwards)

- Sources: PubMed, and internet engine searches (English and French when applicable).
- Efforts have been made to include the year of the study, and not the year of the publication. If they are known to be different, the year of publication is included in the reference.
- For grey literature, links have been included when possible.
- Note that not all papers have been read in full. In many cases, only the abstracts have been read. Critical evaluation of the papers for inclusion has not been conducted.
- Prevalence data is quite limited for some countries, but details on incidence have been found, and they have been included when thought to be relevant.

ASIA

Bangladesh

Year	Area	Species of animal	No. of outbreaks (O), No. of cases (C)	Prevalence	Reference
2012	Nationwide surveillance program	Various	C: 162,051 Buffaloes: 4,596 Cattle: 143,953 Goats: 12,287		Mondal & Yamage, 2014

			Sheep: 1,215		
2011	Nationwide surveillance program	Various	C: 93,968 Buffaloes: 3,187 Cattle: 81,515 Goats: 8,662 Sheep: 604		Mondal & Yamage, 2014
2010-2011	Rajshaji	Cattle: 347		25.07%	Sarker et al, 2011
2010	Nationwide surveillance program	Various	Cases: 44,314 Buffaloes: 1,015 Cattle: 39,694 Goats: 3,444 Sheep: 161		Mondal & Yamage, 2014
2006-2007	Upazila Vet Hospital, Meghna, Comilla	Cattle: 253		24.51%	Mannan et al, 2009

India

Year	Area	Species of animal	No. of outbreaks (O), No. of cases (C)	Prevalence	Reference
2010-2012	Majority of the states	Sheep: 4,407 Goats: 4,035		Sheep: 20.35% Goats: 13.60%	Rout et al, 2014
2010	Orissa	Goats		NSP-Ab: 38% SP-Ab: 20.7%	Ranabijuli et al, 2010
2006-2011	National surveillance Centres	Cattle: 94.5% Buffaloes: 3.3% Pigs: 1.21% Sheep: 0.115%	2,669 outbreaks/cases	Eastern region: 43% Southern region: 31.5% North-eastern region: 11.6%	Subramaniam et al, 2013

				Central region: 5% Western region: 4.4% Northern region: 4%.	
1977-2013	Karnataka	Cattle and buffaloes	O: 11,159 C: 271,000		Hegde et al, 2014

FMD outbreaks recorded in different regions of India and serotypes involved 2006-2011.

Source: Subramaniam et al, 2013

	2006–2007	2007–2008	2008–2009	2009–2010	2010–2011
Southern region					
Tamil Nadu	16(O)	199(O),1(A), 1(Asia1)	–	–	13(O)
Kerala	70(O),10(A), 6(Asia1)	94(O),7(A), 1(Asia1)	15(O),12(A)	19(O),6(A)	8(O)
Karnataka	24(O),9(A)	70(O),21(A)	23(O),1(A)	22(O)	27(O)
Andhra Pradesh	76(O),3(A), 10(Asia1)	47(O),4(Asia1)	13(O)	10(O),2(A)	2(O),1(A)
Northern Region					
Punjab	–	2(O)	3(O),1(A)	1(A)	3(O)
Haryana	1(O)	2(A)	1(Asia1)	1(O), 1(A)	2(O)
Jammu and Kashmir	2(O)	6(O)	10(O)	–	1(O)
Uttar Pradesh	3(O)	6(O), 1(A), 3(Asia1)	2(O),1(A)	36(O), 7(A), 5(Asia1)	2(O)
Himachal Pradesh	1(O)	–	–	1(O)	1(O)
Uttarakhand	+	+	+	2(O),1(A)	+
Central region					
Madhya Pradesh	14(O),9(Asia1)	18(O),5(A), 12(Asia1)	21(O),12(Asia1)	18(O),2(Asia1)	27(O),2(A)
Chhattisgarh	+	+	+	+	+
Western region					
Gujarat	13(O),1(A), 1(Asia1)	9(O),2(Asia1)	6(O)	5(O), 6(Asia1)	5(O),1(Asia1)
Maharashtra	6(O),1(A), 6(Asia1)	11(O),1(A), 5(Asia1)	4(O),1(A), 5(Asia1)	10(O),2(A), 1(Asia1)	6(O),2(Asia1)
Rajasthan	1(A)	2(O),1(Asia1)	–	–	3(O),1(Asia1)
Eastern region					
West Bengal	232(O), 47(A) 120(Asia1)	99(O), 22(A) 15(Asia1)	46(O), 3(A) 4(Asia1)	216(O), 1(A) 1(Asia1)	14(O),4(Asia1)
Bihar	25(O),5(A)	101(O),2(A)	–	137(O)	10(O)
Orissa	2(O)	17(O),2(A)	13(O)	7(O),3(A)	1(O)
Jharkhand	+	+	+	2(O)	+
North eastern region					
Assam	3(A),52(Asia1)	37(O),2(A), 8(Asia1)	14(O)	30(O)	10(O),6(A)
Manipur	2(O)	–	1(O)	2(O)	2(O)
Meghalya	1(O),3(A)	5(O)	3(O)	5(O)	3(O),3(Asia1)
Arunachal Pradesh	–	7(O),4(Asia1)	4(O),1(A), 1(Asia1)	13(O)	6(O),1(Asia1)
Tripura	2(O)	6(O),1(A)	13(O)	15(O)	1(A),4(Asia1)
Sikkim	–	–	–	1(O)	–
Mizoram	1(O)	3(O)	1(O),1(A)	8(O)	1(O)
Nagaland	–	12(O)	4(O)	–	3(O)

–: No outbreak recorded, +: No information available.

Indonesia

Declared its freedom from FMD in 1986, and was recognized by the OIE in 1990.

Myanmar

Year	Area	Species of animal	No. of outbreaks (O), No. of cases (C)	Prevalence	Reference
2010	Sagaing & Tanintharyi			Sagaing: 42% Tanintharyi: 11.7%	Kyaw Naing Oo, 2013

Nepal

Year	Area	Species of animal	No. of outbreaks (O), No. of cases (C)	Reference
2000-2009		Various	Outbreaks by species: Cattle: 42% Buffalo: 32% Goats: 19% Sheep: 4% Pigs: 3% For the number of outbreaks, see Figure 5 below.	Chandra Jha, 2012

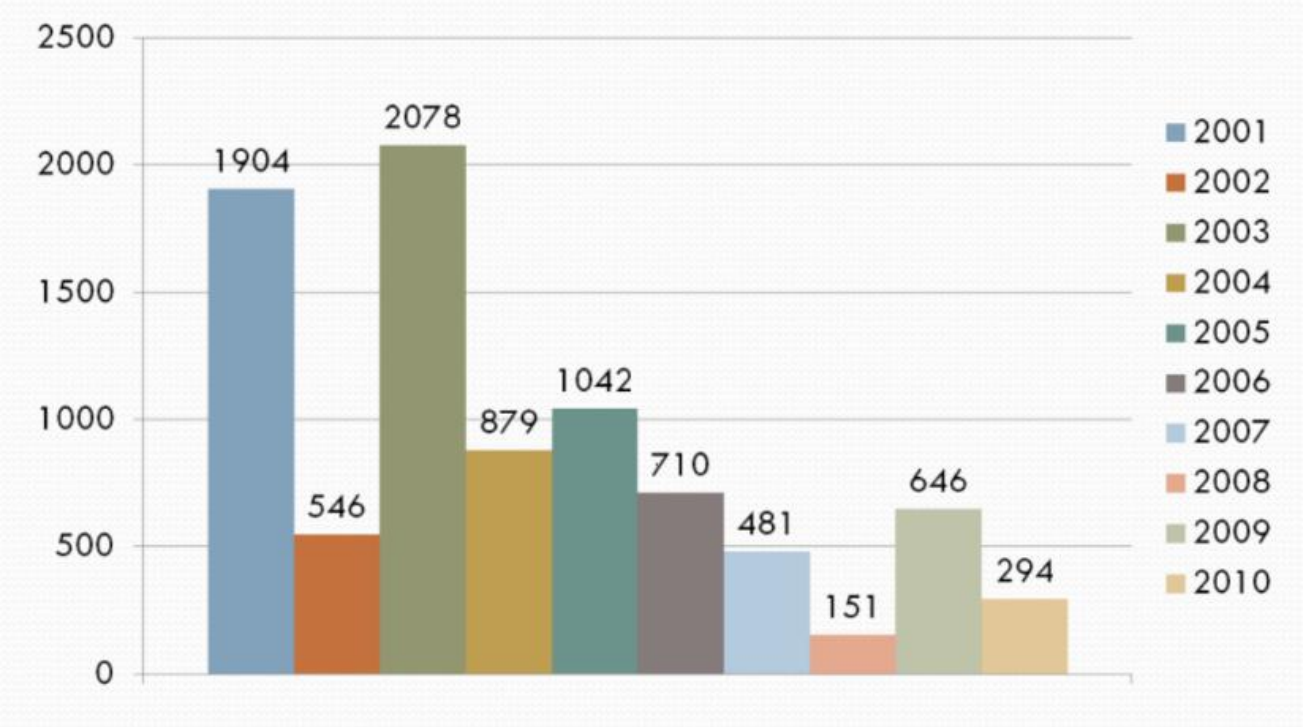


Figure 5: FMD Outbreaks in Nepal 2001-2010
http://www.fao.org/fileadmin/user_upload/eufmd/docs/India_meeting_feb_2012/23_Nepal_FMD_presentation.pdf

Vietnam

Year	Area	Species of animal	No. of outbreaks (O), No. of cases (C)	Prevalence	Reference
2012-2013	LangSon, SonLa and LongAn	Cattle and buffaloes		NSP: 22.3% (previously infected) Probang qRt-PCR: 2.4% (asymptomatic carriers)	Dung et al, 2015 & De Carvalho Ferreira 2015

AFRICA

For details on the epidemiology of FMD in Africa, see Annex 1.

West Africa

In a study conducted in 2006 [3], including three cattle exporting Sahel countries (Burkina-Faso, Mali and Niger) and four cattle importing coastal countries (Benin, Côte d'Ivoire, Ghana and Togo), some FMD risk areas were identified, due to the high density of livestock (see Figure 6):

1. Ivory Coast: North and Central regions
2. Mali: Sikasso, Bamako, Ségou, Mopti, and Asango regions, and the border between Mali-Niger-Burkina-Faso.
3. Burkina-Faso: all the country
4. Niger: Border with Nigéria, Mali, Chad, cure salée región
5. Bénin: Borgou, Atacora and Zou regions
6. Togo: Coastal region, maritime, plateaux, and savanes (border with Burkina-Faso),
7. Ghana: régions de Bawku, Techiman, Tamalé and Ashiama.

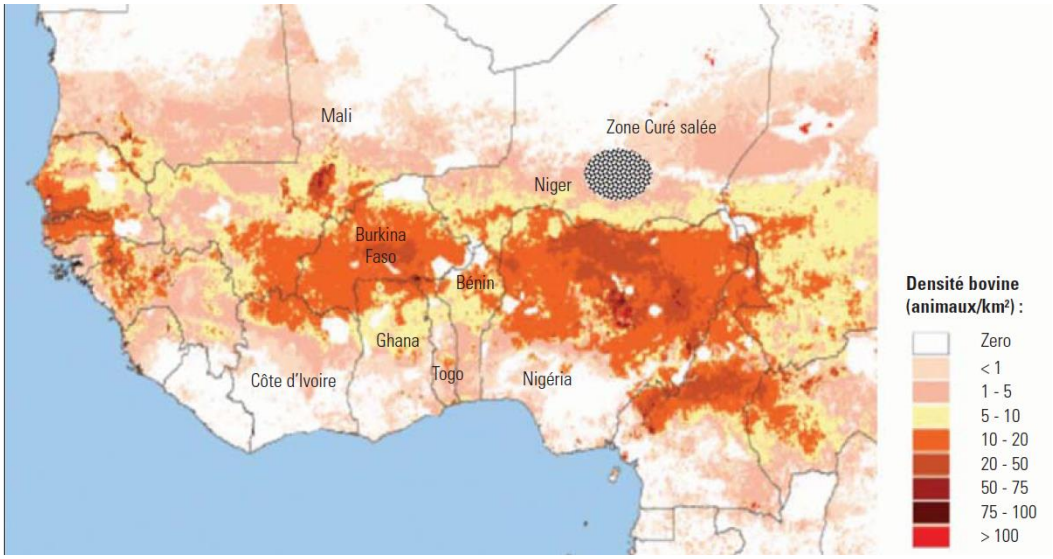


Figure 6: Risk areas for FMD corresponding to areas of high animal density.
Source: Couacy-Hymann et al, 2006 [3]

Commercial and transhumance routes, play a very important role in the diffusion of the disease. Some primary disease focus are: the Benin – Niger – Nigeria border, the Niger – Mali – Burkina Faso border, and the junction Benin-Burkina Faso- Niger (see Figure 7)

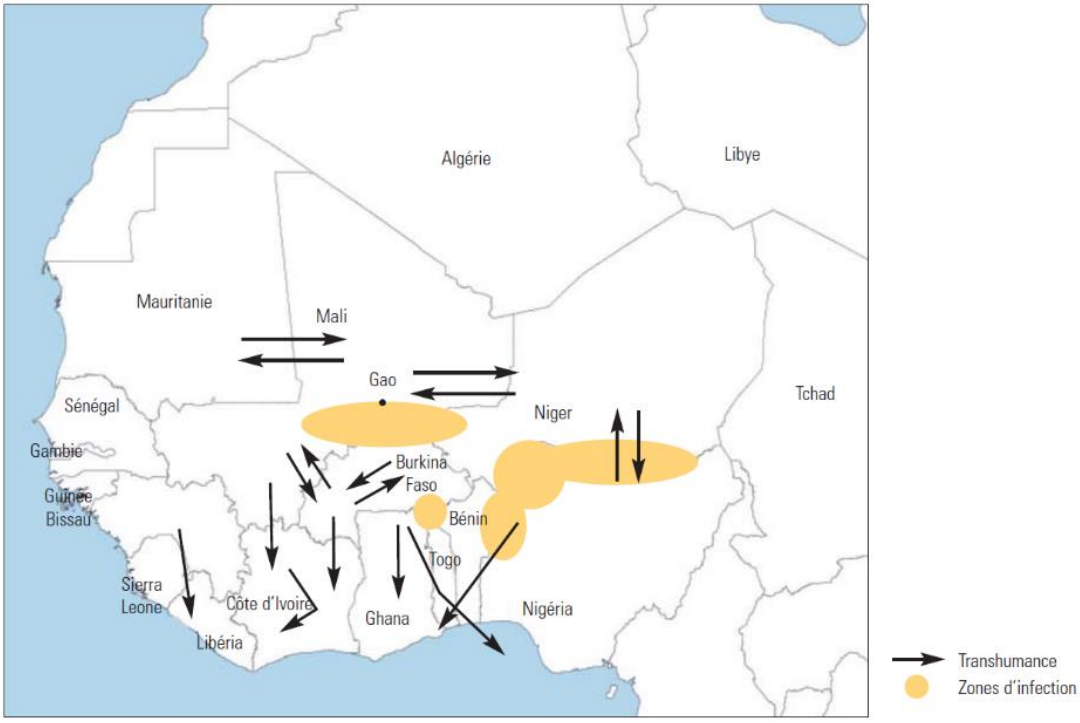


Figure 7: Areas of primary disease. Source: Couacy-Hymann et al, 2006 [3]

Burkina Faso

No data on prevalence was found. However, Burkina Faso is considered a region at risk.

Ethiopia

Year	Area	Species of animal	No. of samples tested	% positive	Reference
2014	Dassenech (South Omo zone)	Cattle	68	10	Molla & Delil 2015
2011	Borana pastoral area	Cattle	768 from 111 herds	Individual: 23	Bayissa et al, 2011

				Herd: 58.6 (3 ABC ELISA)	
2008-2009	Amhara, Oromia, Addis Ababa	Cattle	496	44.2	**Nequsssie et al, 2011**
2008-2009	South Omo zone	Cattle	770	8.18 (3ABC ELISA)	**Molla et al, 2010**
2008-2009	East and West Hararghe zones in Oromiya state	Cattle	504	11.6 (ELISA)	**Yahya et al, 2013**
2007-2008	Bench Maji zone	Cattle	273 in 98 herds	12.08 (3ABC ELISA)	**Gelaye et al, 2009**
2007-2008	Southern Ethiopia	Cattle	1,020 in 79 herds	Individual: 9.5 Herd: 48.1	**Megersa et al, 2009**
2003-2006	Whole country	Cattle	4,465	10.5 (3ABC ELISA) For details see table below	**Ayelet et al, 2012**

Seroprevalence of FMD in different zones of Ethiopia, based on the 3ABC ELISA. Source: **Ayelet et al, 2012**

Region	Zone	No. of sera tested	No. testing positive	Proportion testing positive	95% confidence interval	
Addis Ababa	Addis Ketema	40	0	0	–	–
	Arada	40	1	0.025	-0.026	0.076
	Bole	40	5	0.125	–	–
	Gulele	40	5	0.125	0.017	0.233
	Kirkos	40	2	0.05	-0.02	0.12
	Kolfe Keranyo	40	6	0.15	0.037	0.263
	Lideta	40	2	0.05	-0.02	0.12
	Nefasiklafto	40	4	0.1	0.003	0.197
	Yeka	40	12	0.3	0.15	0.45
Afar	Zone 1	58	0	0	–	–
	Zone 4	299	14	0.047	0.024	0.07
Amhara	Awi	189	8	0.042	0.014	0.071
	North Gonder	101	0	0	–	–
	North Wollo	103	2	0.019	-0.007	0.046
	South Wollo	93	4	0.043	0.001	0.085
Benishangul	Meteket	160	0	0	–	–
Gambella	Itang	160	0	0	–	–
Oromia	Arsi	19	0	0	–	–
	Borena	585	157	0.268	0.233	0.304
	East Harerge	45	4	0.089	0.002	0.176
	East Shoa	80	1	0.013	-0.012	0.037
	Guji	349	114	0.327	0.279	0.374
	Ilubabor	301	10	0.033	0.013	0.053
	North Shoa	173	3	0.017	-0.002	0.037
SNNP	Bench Maji	100	10	0.1	0.047	0.153
	Gomugofa	40	0	0	–	–
	Hadya	160	2	0.013	-0.005	0.03
	South Omo	200	24	0.12	0.077	0.163
	Sidama	160	1	0.006	-0.006	0.019
Somali	Jijiga	66	1	0.015	-0.015	0.045
	Shinile	224	5	0.022	0.003	0.042
Tigray	Central zone	139	37	0.266	0.193	0.339
	Eastern zone	41	17	0.415	0.255	0.574
	Western zone	220	12	0.055	0.025	0.084
Total		**4,465**	**467**	**0.105**	**0.096**	**0.113**

Ivory Coast

No recent information was found.

Kenya

Year	Area	Species of animal	No. of samples tested	% positive	Reference
2010	39 counties	Cattle	3,709	52.5	Kibore et al, 2013
2010	15 counties	PIgs	180	NSP: 54.4 (NSP)	Kibore et al, 2014

2010	Countrywide	Pigs	191	NSP: 53%	Wekesa et al, 2014

Madagascar

Recognized as FMD free by the OIE.

Malawi, Mali, Mozambique, Rwanda and Senegal

No recent data on FMD prevalence was found for any of those countries.

South Africa

South Africa is recognized by the OIE, as having a FMD free zone where vaccination is not practiced (see Section 5). That covers the majority of the country. The Infected zone is mainly the Kruger National Park.

Tanzania

Year	Area	Species of animal	No. samples tested	% positive	Reference
2014	Mikumi, Mkomazi, Ruaha national parks.	Cattle and buffaloes	330	76.3 (3ABC NSP) See details in table below.	Mkama et al, 2014
2014	Serengeti ecosystem, Central part of Tanzania.	Cattle, sheep and goats	Cattle: 361 Sheep: 21 Goats: 11	Overall: 66.25 Wildlife-livestock interface: 71.5. Non interface area: 61 Kongwa: 89%, Serengeti: 78%, Bunda: 65% and Iramba 33%. Cattle: 69.81%, Sheep: 52.38% and goats: 11.11%.	Mdetele and Kassanga, 2014

2010-2011	6 districts in Eastern Tanzania	Cattle	91	Overall: 43.6 (NSP 3ABC) Bagamoyo: 81, Kibaha: 56.2 Kinondoni: 41.7, Ilala: 34.8 Kisarawe: 16.7, Temeke: 15.4	Mwanandota, 2013

FMD seroprevalence in cattle and buffaloes. Source: Mkama et al, 2014

Location	Animal species	Samples tested	Positive samples	Highest PI	Positive samples (%)
Mikumi	Buffalo	30	28	94.24	93.3
	Cattle	35	29	94.82	82.9
Ruaha	Buffalo	31	29	94.95	93.5
	Cattle	53	42	93.56	79.3
Mkomazi	Buffalo	31	7	91.65	22.6
	Cattle	60	35	94.56	58.3
Katavi	Buffalo	29	29	95.10	100
	Cattle	61	49	95.48	80.3
Total	-	**330**	**248**	-	**76.3 (average)**

Uganda

Year	Area	Species of animal	No. of samples tested	% positive	Reference
2014	Isingiro and Nakasongola	Cattle	17 herds	23.6	Baluka et al, 2014
2011	Pastoral herds that closely interact with wildlife around Queen Elizabeth National Park	Cattle	247	15	Dhikusooka et al, 2016
2007	Kasese (K) and Busheny (B)	Cattle, goats and sheep	Cattle: K193, B: 116 Goats: K: 143, B:128 Sheep: K: 57, B: 18	Cattle: K: 61, B: 4 Goats: K: 14, B: 0 Sheep: K: 21, B: 0	Ayebazibwe et al, 2012
2005-2008	National Parks	Various	Buffaloes: 207 Hartebeest: 7 Impalas: 21	Buffalo: 85 Hartebeest: 14.3	Ayebazibwe et al, 2010

			Giraffe: 1 Common eland: 1 Waterbucks: 5	The other animals were all negative	

Zambia

Year	Area	Species of animal	No. samples tested	% positive	Reference
2011-2012	National Parks & Game management areas	Buffaloes	99	92.9 See table below for details	Sikombe et al, 2015

Seroprevalence in buffaloes by liquid phase blocking ELISA. Source: Sikombe et al, 2015

Study area NP/GMA	Number tested	SAT serotype SAT1 %	SAT2 %	SAT3 %	Overall prevalence %	Mixed infection %
Lower Zambezi	25	88.0 (68.8–97.4)	84.0 (63.9–95.5)	8.0 (0.98–26)	100.0 (83.3–100)	84.0 (63.9–95.5)
Lundazi	25	88.0 (68.8–97.4)	100.0 (83.3–100)	12.0 (2.5–31.2)	100.0 (83.3–100)	100.0 (83.3–100)
Mosi-oa-tunya	25	32.0 (14.9–53.5)	76.0 (59.3–92.7)	44.0 (24.4–65.1)	92.0 (74.0–99.9)	60.0 (38.7–78.9)
Sichifulo	20	45.0 (23.1–68.3)	35.0 (15.4–59.2)	50.0 (27.2–72.8)	95.0 (75.1–99.9)	35.0 (15.4–59.2)
Sioma	4	0	0	0	0	0

Economic and Social Impacts at Global and Regional Levels, and in Selected Countries

Although a disease of low mortality, the global impact of FMD is colossal due to the huge numbers of animals affected. The impact of the disease differs considerable in different parts of the world. In the developed world it is the most feared of all animal diseases with the possible exception of those that have zoonotic potential such as BSE. The reason is the devastating economic consequences it can have.

The Taiwan case: Between March and July 1997, FMD struck Taiwan for the first time in sixty years. The particular strain of the virus was "pig-adapted". The disease, which apparently originated on the Chinese mainland, spread like wildfire throughout Taiwan. Over a period of six weeks, FMD virus infected a total of 6,147 pig farms, decimating the country's huge swine industry. The price of Taiwanese pigs dropped 60 percent within a week, and the export market to Japan collapsed. Bringing the epidemic under control required the slaughter of some 4 million pigs at a cost of more than USD 6 billion, and some 50,000 workers in the swine industry lost their jobs. The Taiwanese swine industry never recovered. Before the 1997 outbreak, Taiwan was one the world's leading pork exporters, but today it is a net importer.

http://fas.org/biosecurity/education/dualuse-agriculture/1.-agroterrorism-and-foodsafety/economic-impact-of-fmd-outbreaks.html

The UK case: FMD struck the United Kingdom in 2001 after pigs were fed food scraps that were infected with the virus from a restaurant. The contaminated meat had either been smuggled into Britain or mislabelled with a false certificate of origin. Because the strain of FMD virus sickened pigs but did not cause obvious illness in other susceptible animals, sheep incubating the disease were distributed widely. By the time the outbreak was detected, between 30 and 50 farms throughout Britain had been affected, and the veterinary authorities were quickly overwhelmed. It took six months to contain the outbreak. Efforts by the British authorities to prevent the spread of the disease led to the culling of 6 million animals—4.9 million sheep, 700,000 cattle, and 400,000 pigs. The slaughter of vast numbers of animals (up to 100,000 per day) cost farmers a total of £3.1 billion and caused severe emotional distress. The British government paid £2.5 billion in compensation and for disposal and clean-up costs. Because of reduced tourism and trade, the total cost to the British economy was more than £8 billion (USD 15 billion)

The impact of FMD in endemic countries is more controversial. In many pastoral communities in sub-Saharan Africa where the disease is prevalent and well recognized by livestock owners they often (although not always) ascribe little importance to it. The simple reason is that in extensive production systems dependent on "unimproved" livestock, the disease is usually relatively trivial and the animals recover uneventfully in a week or two. The loss of production in such systems is usually seen as unremarkable, although the disease may result in a lack of draught power for ploughing at critical times and therefore results in agricultural and social disruption. It may also affect production by the growing peri-urban, small-scale diaries developing in many parts of Africa. The lower impact of the disease in SSA may also, to some extent, be due to indigenous cattle having greater inherent resistance than breeds selected in developed countries for high yields. It has been said that in some endemic countries, for small livestock keepers, the control measures are more onerous than the disease itself (for example restrictions in taking their animals to market) but that is influenced by the unappreciated production losses.

Knight-Jones and Rushton in their publication in 2013 [4], estimated that annual impact of FMD in terms of visible production losses and vaccination in endemic regions alone amount to between US$6.5 and 21 billion. In addition, outbreaks in FMD free countries and zones cause losses of >US$1.5 billion a year.

This impact can be separated into two components: [1] direct losses due to reduced production and changes in herd structure; and [2] indirect losses caused by costs of FMD control, poor access to markets and limited use of improved production technologies (Figure 8).

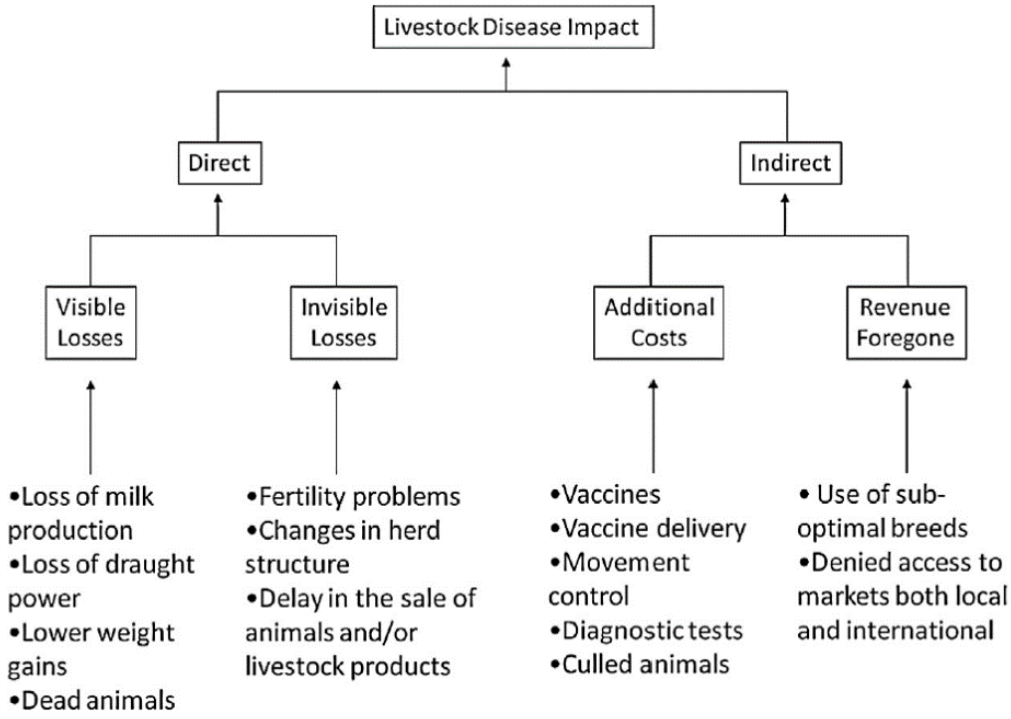


Figure 8: The impact of FMD. Source: Knight-Jones and Rushton, 2013 [4].

Direct Costs

The visible losses are more prominent in pigs and dairy cattle. They include reduced milk production (which can account for 33% of losses in endemic settings), suppressed growth rates, mortality in young animals (can be 2-3%), loss of traction power, and abortions. The invisible losses are mainly due to abortions and reduced conception rates.

Indirect Cots

Control costs: They vary depending on the measures taken by the veterinary services. Additional costs are taken by the private sector (for example vaccination). It is estimated that 2.35 billion doses of vaccine are administered in the world every year (Table 5).

Table 5: Estimated vaccinations by country per year. Source: Knight-Jones and Rushton, 2013.

Region	Vaccinations		Population targeted		
	Doses (millions)	%	Species	Population (millions)	% vaccinated[a]
China	1600	68.1	Cattle, shoats, pigs and buffalo	833	192.2
India	150	6.4	Cattle and buffalo	280	53.6
Rest of Asia	50	2.1	Cattle, pigs and buffalo	283	17.7
Africa	15	0.6	Cattle	272	5.5
Europe and Turkey	15	0.6	Cattle	140	10.7
Middle East	20	0.9	Cattle and shoats	167	12.0
South America	500	21.3	Cattle	342	146.1
Total	2350	100.0		2036	115.4

[a] Calculated as the number of vaccine doses × 100/population size; values >100% imply that on average animals were vaccinated more than once a year.

FMD impacts are not the same throughout the world [4]:

1. FMD production losses have a big impact on the world's poorest where more people are directly dependent on livestock. FMD reduces herd fertility leading to less efficient herd structures and discourages the use of FMD susceptible, high productivity breeds. Overall the direct losses limit livestock productivity affecting food security

2. In countries with ongoing control programs, FMD control and management creates large costs. These control programs are often difficult to discontinue due to risks of new FMD incursion.

3. The presence, or even threat, of FMD prevents access to lucrative international markets.

4. In FMD free countries outbreaks occur periodically and the costs involved in regaining free status have been enormous.

FMD is highly contagious and the actions of one farmer affect the risk of FMD occurring on other holdings; thus sizeable externalities are generated. Control therefore requires coordination within and between countries. These externalities imply that FMD control produces a significant amount of public goods, justifying the need for national and international public investment.

The global FMD impact due to vaccination cost and direct visible production losses can be seen in Table 6. The costs were estimated using variable reported vaccination costs, production losses and uncertain FMD incidence. The variation in total impact is shown (90% range) as well as median estimates. Vaccination costs of between US$0.4 and 3 (most likely US$1) per dose and production losses of between US$100 and 370 (most likely US$100) were used [4].

Table 6: Global FMD impact due to vaccination costs and direct, visible production losses by region. Outbreaks in free countries are not included. Source: Knight-Jones and Rushton, 2013.

	Impact US$			
	Production losses	Vaccination	Total	
Region	Median	Median	90% range	Median
China	1.9 billion	2.2 billion	2.5–7 billion	4 billion
India	1.9 billion	0.2 billion	1–4 billion	2.1 billion
Rest of Asia	1.2 billion	70 million	0.7–3 billion	1.3 billion
Africa	2.3 billion	20 million	1–5 billion	2 billion
Europe and Turkey	35 million	20 million	0.03–0.1 billion	0.06 billion
Middle East	0.2 billion	30 million	0.1–0.5 billion	0.22 billion
South America	0.1 billion	0.7 billion	0.5–1.4 billion	0.8 billion
Total	7.6 billion	2.5 billion	6.5–21 billion	11 billion

Individual country information

For some of the focus countries, information on the impact of FMD is available:

Bangladesh

Momtaz et al 2014, mention that FMD is endemic in Bangladesh, and causes an annual economic loss of USD 60-150 million in Bangladesh.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4219755/pdf/ebo-10-2014-187.pdf

India

Govindraj et al, 2015, conducted a study to assess the impact of FMD outbreaks in cattle and buffaloes on farming community in Kolar district, Karnataka state, India. Primary data were collected from 178 sample farms. The results showed that 78% of surveyed villages were affected with FMD.

In indigenous cattle, the highest loss due to FMD was distress sale (208 USD) followed by other losses, whereas, in crossbred cattle, the highest loss was mortality loss (515 USD) followed by distress sale (490 USD), milk yield loss (327 USD), treatment cost (38 USD) and extra labour engagement expenses for nursing of FMD-affected bovines (30 USD) – all costs are per animal.

In local and upgraded cattle, the mean total loss per affected animal was 521 USD and 1941 USD, respectively. In local and upgraded buffaloes, the mean total loss per animal was 639 USD and 1008 USD, respectively. Table 7 below shows the average losses due to milk yield reduction, draught power, treatment, mortality and distress sale for FMD-affected animals in Karnataka (USD/animal).

As per the social impact, the majority of the livestock owners perceived FMD had caused permanent asset loss, which in turn increased psychological stress of the family.

In a presentation by Ganesh Kumar, Project Directorate on Animal Disease Monitoring and Surveillance Bangalore (year not stated, but probably around 2010-2011) he explained that the total direct impact of FMD in farms in areas where there was a control program was R 41,482 (USD 892), and in farms with no control program was Rs. 63,768 (USD 1,372). Indirect losses were not quantified. It was also projected that the state of Andhra Pradesh would stand to lose Rs. 1,147 crores (Rs. 11,470 million, approx. USD 247 million) on account of direct impacts, if there was no vaccination programme against FMD. Similarly, the country would incur a total direct loss of Rs. 15,575 crores (155,750 million, approx. USD 3,351 million). The indirect costs would be much more than this.

http://www.fao.org/docs/eims/upload/299846/an367e00.pdf

Table 7: Average losses due to milk yield reduction, draught power, treatment, mortality and distress sale for FMD-affected animals in Karnataka (USD/animal). Source: Govindaraj et al, 2015 [5].

Species	Scenario	Milk yield loss (Total)	Draught power loss	Treatment cost	Mortality loss	Extra labour expenses	Distress sale	Total loss
Indigenous cattle	I	83 (57–108)	40 (19–55)	33 (7–92)		30 (12–225)	208 (208–208)	521
	II	90 (67–116)	42 (23–59)	35 (12–96)		32 (14–229)	218 (218–218)	541
	III	74 (50–97)	38 (17–51)	40 (5–87)		29 (9–223)	206 (206–206)	512
Crossbred cattle	I	327 (31–1022)		38 (17–292)	515 (83–1042)	30 (12–225)	490 (12–1225)	1941
	II	340 (38–1038)		40 (23–298)	541 (87–1051)	32 (14–229)	515 (16–1248)	2013
	III	315 (24–1004)		36 (14–284)	489 (76–1033)	29 (9–223)	488 (6–1216)	1899
Local buffalo	I	89 (22–199)		34 (16–150)	209 (8–500)	30 (12–225)	78 (18–175)	639
	II	96 (29–199)		36 (21–158)	219 (15–517)	32 (14–229)	82 (23–183)	660
	III	82 (17–189)		32 (11–143)	199 (5–492)	29 (9–223)	77 (13–164)	622
Upgraded buffalo	I	186 (186–186)		22 (20–45)	275 (275–275)	30 (12–225)		1008
	II	207 (207–207)		23 (23–49)	289 (289–289)	32 (14–229)		1035
	III	197 (197–197)		21 (16–41)	261 (261–261)	29(9–223)		982
		F (3,205) = 12.4, (P = 0.000)		F (3,338) = 3.8, (P = 0.01)	F (3,146) = 9.8, (P = 0.000)		F (2,21) = 2.6, (P = 0.09)	

F-test was carried to know the significance difference across species in scenario I; Figures in parentheses indicate range values.

Nepal

Economic losses due to FMD infection in Nepal, have been estimated to be about USD 5.36 million per year. A study of the economic impact of livestock diseases in rural areas of Nepal estimated that FMD could account for 26% of the overall economic losses in livestock production. (Quoted by **Chhetri et al, 2010**).

Ethiopia

Jemberu et al, 2014, assessed the impact of FMD in Ethiopia based on data obtained from case outbreaks in cattle in crop-livestock mixed and pastoral smallholder farming systems that occurred in 2012 and 2013. FMD morbidity rates of 85.2% and 94.9% at herd level; and 74.3% and 60.8% at animal level in the affected herds were determined for crop-livestock mixed system and pastoral system, respectively. The overall and calf specific mortality rates were 2.4% and 9.7% for the crop-livestock mixed system, and 0.7% and 2.6% for the pastoral system, respectively. Herd level morbidity rate was statistically significantly higher in the pastoral system than in the crop-livestock mixed system (P<0.001). The economic losses of and FMD outbreak due to milk loss, draft power loss and mortality were on average USD 76 per affected herd and USD 9.8 per head of cattle in the affected herds in crop-livestock mixed system; and USD 174 per affected herd and USD 5.3 per head of cattle in the affected herds in the pastoral system. The herd level economic losses were statistically significantly higher for the pastoral system than for the crop-livestock mixed system (P<0.001). The major loss due to the disease occurred as a result of milk losses and draft power losses whereas mortality losses were relatively low. Although

the presented estimates on the economic losses accounted only for the visible direct impacts of the disease on herd level, these conservative estimates signify a potential socioeconomic gain from a control intervention.

Knight-Jones and Rushton 2013, estimated the impact of FMD in different epidemiological and trade situations. As example of an endemic country with the potential to export, they presented Ethiopia:

Ethiopia has the largest cattle population in Africa; in 2006 there were >43 million cattle with slightly fewer sheep and goats. Large numbers of ruminants are exported; in the Ethiopian financial year (July 2010–July 2011), meat and livestock export revenue was $211.1 million, mostly from live animal trade with the Middle East (>472,041 heads of live animals,70% of which were cattle). However, production costs are high compared to other meat exporting nations, such as Australia or Brazil, limiting the potential for export market access regardless of FMD status. Difficulties in meeting export Sanitary and Phyto-Sanitary standards results in greater numbers of livestock being purchased by traders for export through unofficial channels where prices are lower. Due to the presence of FMD and other OIE listed trade limiting diseases the export of live cattle and their products to FMD free countries is an unlikely prospect. This raises the case for investment in veterinary service infrastructure to improve the control of all trade limiting diseases for international market access. Having an economy that is highly dependent on smallholder and animal-based agriculture, including the widespread use of beasts of burden, the direct impacts of FMD are substantial in Ethiopia. In agro-pastoral areas, FMD infected oxen are unable to work for the entire season when affected at cropping time. Pastoralists are particularly vulnerable to FMD as their living depends entirely on their livestock. By reducing the supply of milk FMD impacts on food security, particularly when outbreaks occur during times of the year when other food sources are limited and dependency upon milk is greatest.

Kenya

Lyons et al 2015, used individual animal data from a large-scale dairy farm in Kenya to estimate the impact of an FMD outbreak due to serotype SAT2 virus on milk yield in an endemic setting. Daily milk yields from 218 mainly European-breed cattle that were lactating during the 29-day outbreak period were considered in the analysis. At the herd level, the average daily yields decreased from around 20 to 13kg per cow, recovering approximately 2 months after the commencement of the outbreak. No difference was found between reported clinical and non-clinical cases suggesting inaccurate case recording, poor sensitivity of the case definition and subclinical infections being present. To further investigate the impact of FMD, yields were predicted for each individual animal based on historic data from the same herd. For cattle lactating during the outbreak, comparisons were made between actual and predicted yields from the commencement of the outbreak to 305 days lactation using a linear regression model. Animals produced significantly less than predicted if in parity 2 or greater and between 0 and 50 days in milk (DIM) at the start of the outbreak period. The maximum effect was seen among animals in parity ≥4 and between 0 and 50 DIM at the start of the outbreak, producing on average 688.7kg (95%CI 395.5, 981.8) less milk than predicted for their remaining lactation, representing an average 15% reduction in the 305 day production for these animals. Generalisation of the results requires caution as the

majority of Kenyan milk is produced in smallholder farms. However, such farms use similar genetics and feeding practices to the study farm, and such systems are increasingly important in the supply of milk globally.

In another paper, also **Lyons et al 2015**, reported the impact of an FMD (virus serotype SAT2) outbreak on a large-scale dairy farm in Nakuru County, on clinical mastitis and culling rate (presumably, the same farm as above). A cohort approach followed animals over a 12-month period after the commencement of the outbreak. Univariable analysis showed FMD cases were culled sooner but there was no effect on clinical mastitis. After adjusting for possible confounders and inclusion of time-varying effects there was weak evidence to support an effect of FMD on culling (HR = 1.7, 95% confidence intervals [CI] 0.88-3.1, P = 0.12). For mastitis, there was stronger evidence of an increased rate in the first month after the onset of the outbreak (HR = 2.9, 95%CI 0.97-8.9, P = 0.057).

Mali

In Mali, the losses due to FMD (milk, meat, draught, cost of treatment) have been calculated to USD 600,000 per year. Referenced by Traore, 2010.

http://www.fao.org/fileadmin/user_upload/eufmd/docs/Vienna_2010/071-App71_FMD_in_Mali_and_West_Africa.pdf

Uganda

Baluka et al 2014, looked at the economic important of FMD in Isingiro district. They estimated the financial losses and economic costs associated to FMD in 17 herds. Three, nine and five herds were selected to represent small (10-50 heads of cattle), medium (51-150) and large herds (151-350 heads of cattle) respectively. The table below shows the annual economic cost of FMD in USD.

During FMD outbreaks and associated quarantine period, more farmers with small and medium herds made losses because they were compelled to sell cattle at salvage sale prices due to lack of alternative sources of income for paying for drugs and vaccination or made distress sales in fear of losing the remaining cattle. Farmers with large herds neither incurred salvage nor mortality losses. Farmers with large herds experienced lower prevalence probably because they have alternative sources of income and can afford to pay for vaccination and buy drugs without having to sell their cattle at salvage prices.

Large herds suffered higher milk losses during FMD outbreaks due to reduction of milk production, sale loss due to no sales and milk sale loss due to quarantine than either the small or medium herds. This is probably because many farmers with large herds have improved their breeds for milk production and in the absence of FMD, large herds sell more milk and earn more income from sale of milk than either small or medium herds.

Table 8: Annual economic cost of FMD in USD in case study herds in Isingiro district. Source: Baluka et al, 2014**.**

Item	Small	Medium	Large
Mortality	595	298	0
Salvage sale loss	198	1571	0
Milk loss	371	874	3708
Treatment	298	635	655
Vaccination	6	34	103
Veterinary costs	8	8	8
Total	1476	3419	4474
Annual economic cost per head of cattle	123	41	17

Zambia

Sinkala et al 2014 [6], looked at the impact of FMD on the Zambian economy, based on Knight-Jones and Rushton framework [4]. Impacts include losses in income of over US$ 1.6 billion from exports of beef and sable antelopes and an annual cost of over US$ 2.7 million on preventive measures:

Direct visible losses: During the 2004 Kafue flats Namwala outbreak, the calving rate reduced during the calving season as most cows did not conceive (Musso Munyeme, personal communication). Herdsmen had earlier observed that the bulls were failing to mount the cows during heat periods because of sores on the feet. On average around 300,000 calves are born every year in this region. During the 2008 outbreak of FMD at a commercial farm in Mazabuka district, milk production was reported to have dropped from 25.5 to 0.5 litres per cow per day (Martin Ndhlovu, personal communication). In Zambia, traditional farming using draught power accounts for the largest production of crops. Elsewhere oxen have been observed to stay off plough for the whole season when outbreaks occur in a cropping season with drop in draught power of 60–70% after one month following infection.

Direct invisible losses: Low conception rates of 52 to 69%, calving rates averaging 40 to 58%, and long calving to conception intervals of 18 to 20 months characterize the reproductive efficiency in Zambia. This may be a result of endemic FMD infections. Fertility reduces because of increase in abortion rates of up to 10% and prolonged inter-calving interval by 12 months due to delays in conception.

Indirect impacts: It is estimated that the Zambian Government spends over US$ 2.7 million yearly on procuring vaccines and conducting and monitoring vaccination campaigns. Biannual vaccination campaigns conducted each year consume the productive time of both the farmer and the field extensive officers to invest in other productive activities. With respect to government cost of control, it is estimated that the cost of erecting and maintaining one checkpoint during the 2004 Namwala outbreak was US$ 10,000 for two weeks. This figure may rise if the period is longer and sometimes three or more checkpoints were required. The cost of surveillance, extension, and farmer training in disease identification and awareness adds to expenditure.

Internal market constraints: In Zambia, demand for beef is the highest in Lusaka with a human population of 2,196,996 and the Copper belt with 1,958,623. During disease outbreaks, movement restrictions imposed on livestock from affected regions create a deficit that leads to upswing of prices of beef and competing goods. Zambia currently imports beef to satisfy local market demand and any drop in the local source worsens the situation. Another consequence of being a country with endemic FMD is that Zambia cannot participate in international livestock trade. For example, as a result of the 2010 Mbala serotype O outbreak, Botswana imposed a total ban on import of maize bran from Zambia. Zambia exports in excess of 30,000 metric tons of maize bran annually to Botswana. It is further estimated that over US$ 3 Million was lost in revenue during the ban (George Phiri, Grain Traders Association, personal communication). In 2008, over 500 sable antelopes could not be exported to South Africa because of trade politics related to FMD. Losses in income from exports of these prime sable antelopes have been estimated at US$ 35 million annually. The loss in income from potential exports of beef and dairy products if a disease free zone existed has been estimated to be over US$ 1.6 billion per annum.

Effect on the internal economic growth: The period between 2000 and 2010 was characterised by increase in the numbers of FMD outbreaks in comparison to previous decades. During the same period, the Zambian human population was increasing at an average of 2.8% per annum. The cattle decline experienced in the early 2000s was probably due to droughts and eventual FMD outbreaks on the Kafue flats. The reduction in calving and conception rates alluded to earlier may have contributed. Even though the country recorded an upswing in cattle numbers from 2,381,421 in 2005 to 2,559, 953 in 2010, the growth was not commensurate with the human population growth. Probably the extension of the 2004 Namwala outbreak to 2005 and 2006 as well as the 2007 to 2009 Mwandi outbreak in the middle Zambezi basin may have contributed. Zambia also experienced positive economic growth in real GDP from 2000 to 2010, but the economic growth was slow to support the population growth. This was mainly because the growth was driven by improved performance in mining and construction sectors while agriculture upon which 80% of the population depends did not perform well, recording relatively low average growth rates, inadequate infrastructure, and poor market access.

Disease Prevention and Control Methods

FMD is a highly contagious viral disease. It has been eradicated in many countries, and in those countries control is based in preventing the disease (re)entering the country. In endemic regions, control will vary depending on the presence of FMD in the wildlife population, and also the presence of a FMD control program.

Import regulations help prevent FMDV from being introduced from endemic regions in infected animals or contaminated foodstuffs fed to animals. Waste food (swill) fed to swine is a particular concern. Heat-treatment can kill FMDV and reduces the risk of an outbreak; however, some countries have completely banned swill feeding, due to difficulty in ensuring that adequate heat-treatment protocols are followed. Protocols for the inactivation of FMDV in various animal products such as milk products, meat, hides and wool have been published by the OIE. Global FMD control programs have recently been established to reduce virus circulation and the incidence of this disease.

Measures taken to control an FMD outbreak include quarantines and movement restrictions, euthanasia of affected and exposed animals, and cleaning and disinfection of affected premises, equipment and vehicles. Additional actions may include euthanasia of animals at risk of being infected and/or vaccination. Infected carcasses must be disposed of safely by incineration, rendering, burial or other techniques. Rodents and other vectors may be killed to prevent them from mechanically disseminating the virus. People who have been exposed to FMDV may be asked to avoid contact with susceptible animals for a period of time, in addition to decontaminating clothing and other fomites. Good biosecurity measures should be practiced on uninfected premises to prevent entry of the virus.

Vaccination may be used to reduce the spread of FMDV or protect specific animals (e.g. those in zoological collections) during some outbreaks. The decision to use vaccination is complex, and varies with the scientific, economic, political and societal factors specific to the outbreak. Vaccines are also used in endemic regions to protect animals from illness. FMDV vaccines only protect animals from the serotype(s) contained in the vaccine. For adequate protection, the vaccine strains must also be well matched with the field strain.

Experimentally, interferon has been evaluated to stop the disease while the immunity elicited by vaccination develops. **http://www.ars.usda.gov/is/pr/2013/131203.htm**.

Wildlife transmission may need to be considered in some locations. One important issue is the persistence of FMDV in wild African buffalo, which may make eradication unfeasible in some areas. In southern Africa, transmission from African buffalo has been controlled by separating wildlife reserves from domesticated livestock with fences, and by vaccination of livestock. However, wildlife fencing may not be practical in some areas, and there are also some disadvantages to its use. Another issue is the protection of highly susceptible wildlife species from FMDV. Vaccination of livestock was reported to decrease outbreaks in some populations, such as saiga antelope.

Treatment (Control)

There is no specific treatment for FMD, other than supportive care. Treatment is likely to be allowed only in countries or regions where FMD is endemic.

Prophylaxis (Prevention)

In order to reduce the FMD disease burden, the FAO and the OIE developed a 15-year global control strategy in 2012 (Figure 9).

Since the global FMD control strategy was brought to light, several initiatives were made to establish an enabling environment to make FMD control a feasible option particularly for countries where the disease is most prevalent. Progressive control pathway for FMD (PCP-FMD) was developed in 2008 and published in 2011 by FAO and EuFMD and became a joint FAO-EuFMD-OIE guiding tool for the national control approach in which standard control measures are applied in a step-wise and monitored manner. PCP document: **http://www.fao.org/ag/againfo/commissions/docs/PCP/PCP-26012011.pdf**

Out of 87 FMD-affected nations, at least 60 are currently engaged at various levels in the implementation of PCP-FMD in the quest to reduce or eliminate FMD virus circulation by 2027. Some regions are making progress in FMD Control, such as South America and South East Asia. However, still a number of countries in Asia, Middle East and Africa are endemic for FMD.

The PCP includes criteria for describing the FMD risk management of countries that are not-free of FMD. It has led to a tool that can be applied to measure (and communicate) country progress within regional roadmaps, and aims at starting countries along a pathway of activities from measuring risk to risk management, covering the stages before they could apply for recognition of disease freedom.

The PCP recognises that differences in risk of infection occur between (and within) infected countries, that countries are at different stages in managing the risk of infection. The PCP applies a risk reduction approach in which each Member State is encouraged to develop national risk reduction strategies that are supportive to the regional effort.

The PCP stages are summarized in Figure 10. The 'Stage Focus' represents overall objective or aim of the stage, and each Stage Focus has a number of 'key outcomes' necessary to achieve that aim. Countries are able to decide for themselves how far, and how fast, it is appropriate for them to progress along the PCP. The Stage Focus therefore does not necessarily assume that a country will progress to the next stage. In order to be placed in a Stage, the country must have achieved all of the key outcomes from the previous Stage, plus have met the minimum requirement for inclusion in the current Stage. Completion of a Stage depends on the attainment of a specific 'indicator' outcome that the country is ready to move to the next Stage. The indicator for each Stage is also described in Figure 10. The PCP approach is not intended to be prescriptive and particularly in the lower Stages it is usually possible to realise the key outcomes through different activities or combinations of activities.

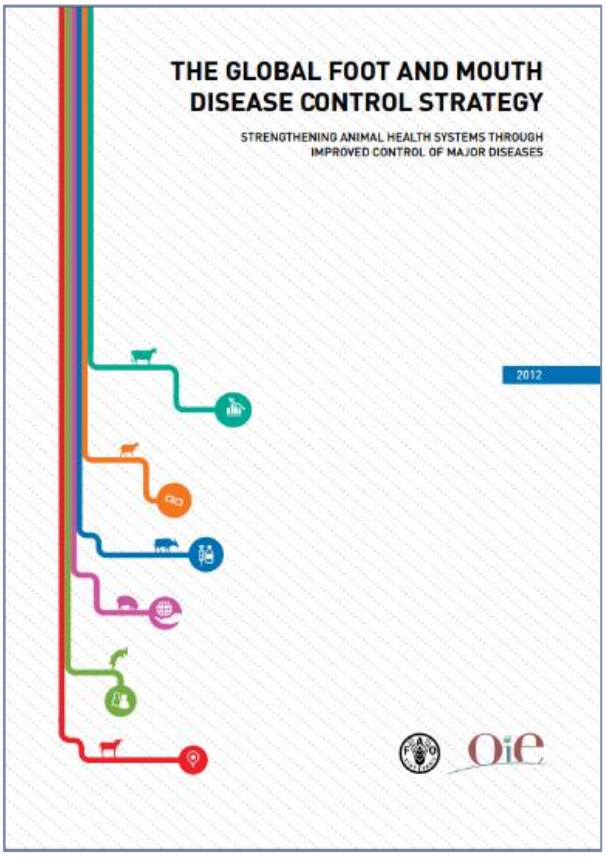


Figure 9: Global FMD control strategy. FAO & OIE, 2012. (click on figure for the link)

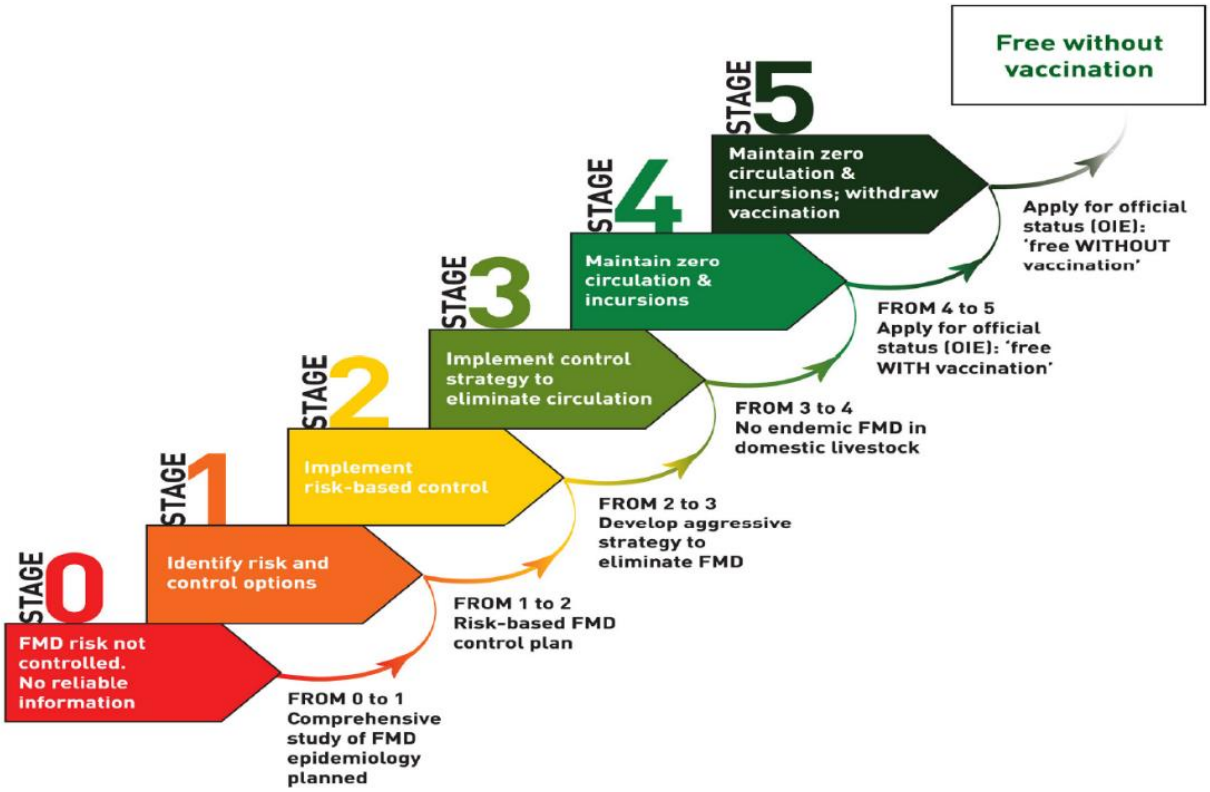


Figure 10: Stage progression in the FMD Progression Control Pathway. Source: PCP-FMD. FAO, EuFMD, FAO.

For an effective implementation of the global FMD strategy and to resolve some of the anticipated challenges, regional roadmap platforms have been successfully used to assess the progress of FMD control in accordance to PCP-FMD guidelines. According to genetic and antigenic analyses, FMD viruses currently circulating have been sub-divided into seven regional pools (Figure 2). As distinctive virus strains tend to occur within a defined region, regional roadmaps have been established in five of the seven regional virus pools (2-6). The FMD roadmap meetings are aimed at sharing information on FMD virus circulation in the region, assessing the progress of each country along the Regional Roadmap and working with them on preparing their national control programmes, project proposals and submissions to OIE for programme endorsement.

Link to roadmaps status in Asia: **http://www.rr-asia.oie.int/activities/regional-programme/fmd/oiejtf-project-for-fmd-control-in-asia/**

Figure 11 shows the different PCP stages of countries in Africa in 2014. Figure 12 shows the Global PCP-FMD map in 2015. [Note: Figure 11 has been included, as some African countries are not assessed in Figure 12].

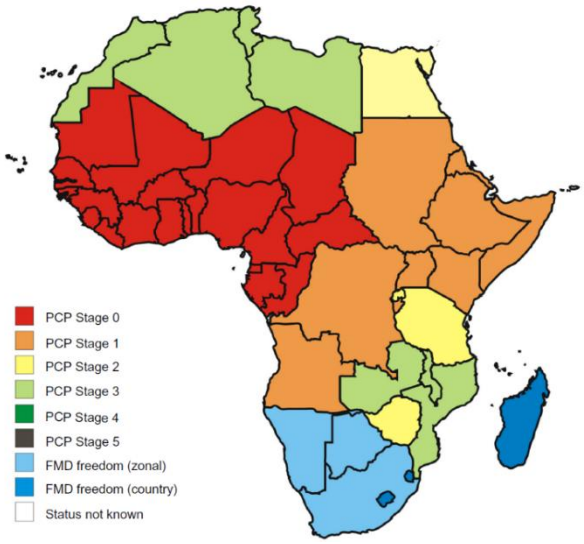


Figure 11: PCP stages in Africa. Source: Maree et al, 2014 [7]

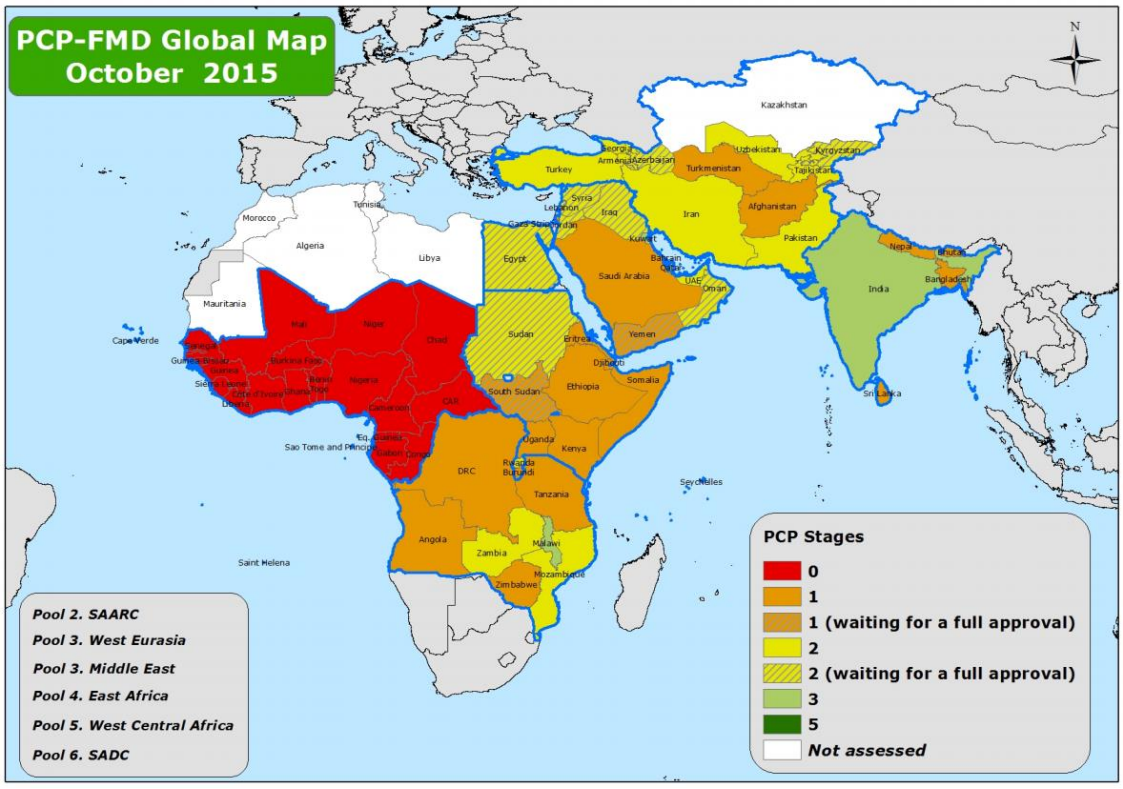


Figure 12: PCP-FMD, Global Map, October 2015. Source: Status of Global FMD Control Programs. Dr Samia Metwally, FAO. Presented at GFRA Scientific meeting, Hanoi 205. Link.

Options and strategies for control programs at national, sub-national or regional level

The AU-IBAR, has developed standard methods and procedures (SMPs) for control of FMD in the Greater Horn of Africa, which includes a section in Control, that covers vaccine, vaccine quality control, vaccine use and registration, procedure for vaccination, disease control planning, preparedness planning, rapid response plan, and recovery plan (pages 19-22 of the following link: **http://www.au-ibar.org/component/jdownloads/finish/76/2118**)

Regional communities in Africa such as the Southern African Development Community (SADC), have also been working on FMD control, supporting PCP: **http://www.oie.int/doc/ged/D10576.PDF**

At country level, many countries have their own control programs, and different regions or provinces might be at different stages. It is not intended to present them here in detail. Only India and South Africa are mentioned as examples.

Control Program in India:

India has an OIE endorsed official control program, as per OIE resolution May 2015. The districts in which a Control Program (CP) is in place, can be seen in Figure 13 below.

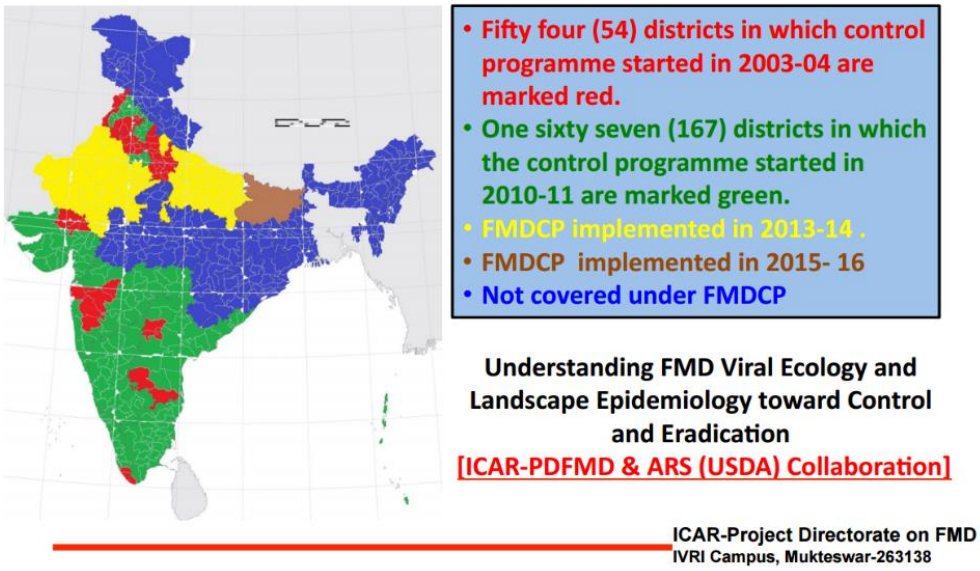


Figure 13: FMD control program in India. Source: Ranjan et al. **Understanding FMD viral ecology and landscape epidemiology toward control and eradication FMD in India. GFRA Scientific Meeting, Hanoi, 2015.**

Control Program in South Africa:

South Africa is recognized by the OIE, as having a FMD free zone where vaccination is not practiced. There is an infected zone (red in the map – Figure 14 below) which includes mainly the Kruger National Park, a protected zone (yellow) and a high surveillance area (dark blue).

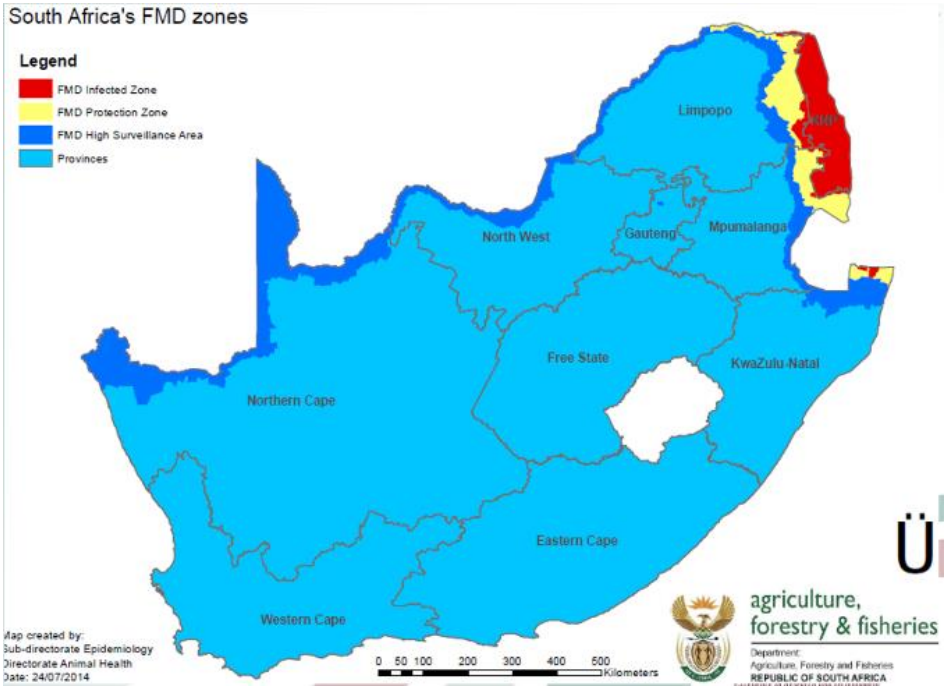


Figure 14: FMD in South Africa. Source: Scott et al, 2015**. Engineering tailor made FMD vaccines for Africa with increased thermostability. Presentation at GFRA Scientific Meeting, Hanoi 2015.**

Rationale for control

If money is spent on disease control, the intention is to reduce losses elsewhere by a greater amount. These losses may be due to reduced production or restricted market access [4]. To control FMD governments must create an environment where population level control costs reflect the benefits experienced by the livestock sector and the wider economy. This requires a combination of:

• Investments in veterinary services, education, research and general infrastructure to develop the animal health system – what economists would call fixed costs.

• Specific programs that cover the costs of FMD control and management – what economists would call variable costs.

In many countries there is already a fixed cost investment in animal health systems, and adding an FMD control program is relatively easy. However, countries that have low level investments in animal health will struggle to implement an effective FMD control program. In this situation there needs to be an increase in both the fixed and variable costs. The fixed cost element will generate capacity and skills that will benefit the control of other diseases and therefore not all costs for this element should be assigned to FMD.

There are many cost benefit analysis studies of FMD control and eradication. A summary as compiled by Knight-Jones and Rushton 2013, is showed in Annex 3.

In cases of outbreak control, is important to evaluate the different outcomes and costs. For example, Figure 15 below, compares the costs and outcomes of FMD outbreaks in UK and Uruguay in 2001.

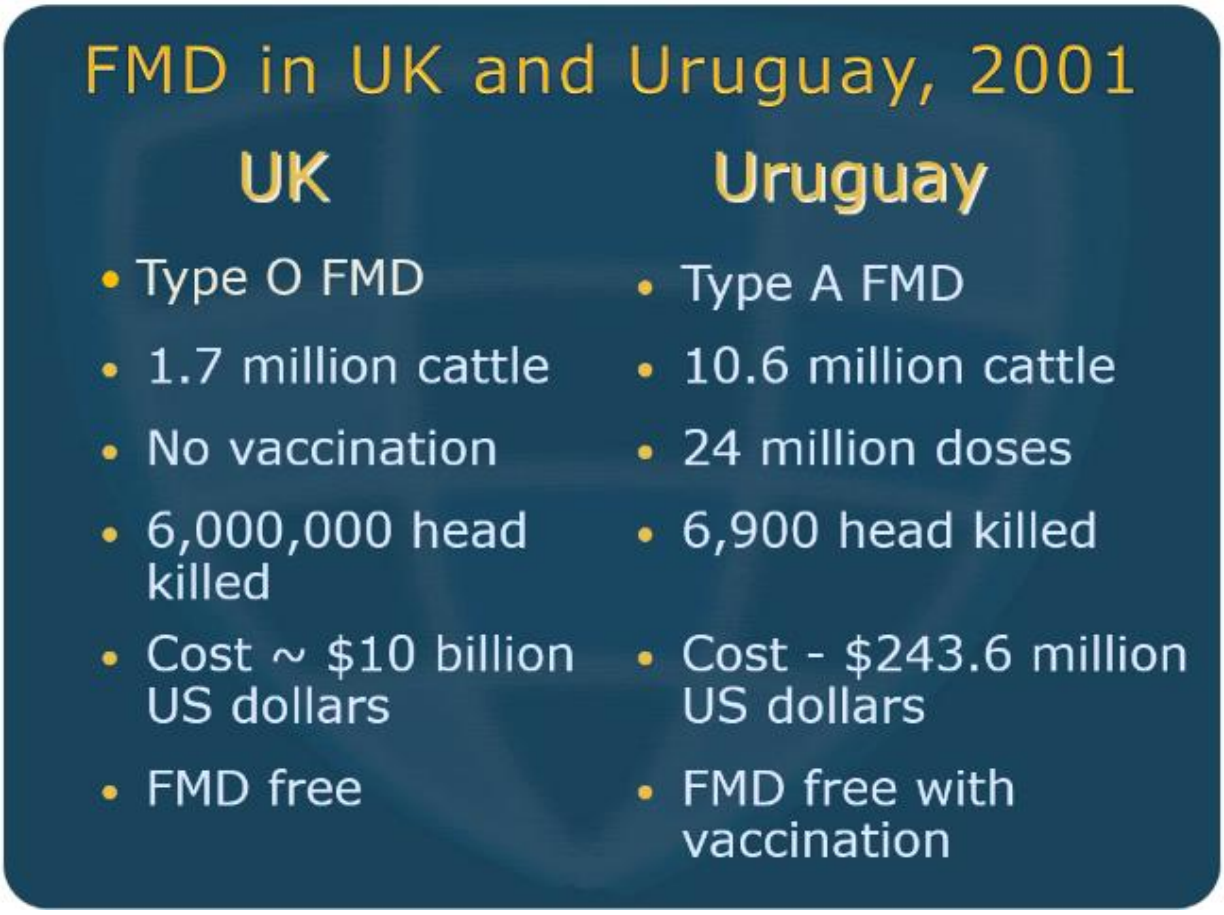


Figure 15: Comparison UK and Uruguay FMD outbreaks in 2001. Source: Roth, 2014. FMD vaccination: Preparedness, availability and limitations**.**

Disease situation and government policies by country:

Tables 9 and 10 below have been completed with the information received so far from the questionnaires sent to the DG and DVS. This information will be updated and completed once the results from the different countries are received. The list of respondents is included in Annex 4.

Table 9 covers the disease situation (if it is notifiable or not), the presence of official surveillance and/or control programs, and the treatment situation. Table 10 refers to vaccination.

The definitions that were given to the respondents are:

[1]Surveillance: is the systematic ongoing collection, collation and analysis of data and the timely dissemination of information to those who need to know so that action can be taken.

[2]Control: a program which is approved, and managed or supervised by the Veterinary Authority of a country for the purpose of controlling a vector, pathogen or disease by specific measures applied throughout that country, or within a zone or compartment of that country.

Table 9: Official status, official programs and treatment for bovine FMD in the countries of interest. Information provided by the questionnaire sent to the DG/DVS as part of this monograph.

Country	Notifiable (yes/no)	Official surveillance[1] program (yes/no) (if yes, active or passive)	Official control[2] program (yes/no)	Treatment (Chemotherapy)	
				Treatment authorised (yes/no)	Frequently practiced (yes/no)
ASIA					
Bangladesh	Yes	Yes, passive and targeted	Yes (limited to some districts)	Yes	Yes
India					
Indonesia					
Myanmar (Burma)	Yes	Yes, passive	Yes	No	Yes
Nepal	No*	Yes, active	Yes	N/A	N/A
Vietnam	Yes	Yes, active	Yes	No	Yes

AFRICA					
Burkina Faso					
Côte d'Ivoire (Ivory Coast)	Yes	Yes, passive but active if outbreak	Yes	Yes	If animals are sick
Ethiopia					
Kenya	Yes	Yes, passive	Yes. Control strategy in place	No	No
Madagascar					
Malawi	Yes	Yes, passive and active	Yes	N/A	N/A
Mali	Yes	Yes, passive	Yes	No	No
Mozambique					
Rwanda	Yes	Yes, active and passive	Yes	No	No
Senegal					
South Africa					
Tanzania	Yes	Yes, passive and active	Yes	No	No
Uganda	Yes	Yes	Yes	Yes (secondary infections)	Yes
Zambia	Yes	Yes, active	Yes	No	No

Data has been entered as to reflect information as provided by the respondents.

*: It is surprising that FMD is not notifiable in Nepal, having an official surveillance and an official control program in place. It might be a mistake in the form, but has not been confirmed.

Table 10: Vaccination for bovine FMD in the countries of interest.
Information provided by the questionnaire sent to the DG/DVS as part of this monograph.

Country	Vaccination			
	Compulsory vaccination (yes/no)	Who pays for the vaccine (Government, farmers, combination, others-specify)	Who delivers the vaccine (official, private vaccinators or both)	Species vaccinated (cattle, sheep, goats, pigs, poultry)
ASIA				
Bangladesh	No	Combination: government subsidy, owner pays service charge	Government & private	Cattle and buffalo
India				
Indonesia				
Myanmar (Burma)	No	Government	Official	Cattle, sheep, goats, pigs
Nepal	No	Combination	Both	Cattle, buffalo, sheep and goats
Vietnam	Yes	Government and farmers	Both	Cattle, buffaloes
AFRICA				
Burkina Faso				
Côte d'Ivoire (Ivory Coast)	No	Farmer	Private	Cattle, sheep and goats
Ethiopia				
Kenya	As per national strategy	Combination	Both	Cattle
Madagascar				

Malawi	Yes	Government	Official	Cattle
Mali	No	Combination	Official	Cattle
Mozambique				
Rwanda	Yes	Government	Official	Cattle
Senegal				
South Africa				
Tanzania	No	Combination	Both	Cattle
Uganda	No	90% Government	Official (<90%)	Cattle
Zambia	Yes	Government	Official	Cattle

Data has been entered as to reflect information as provided by the respondents.

Vaccines Available

According the OIE Terrestrial Manual, **traditional FMD vaccines** may be defined as a fixed formulation containing defined amounts (limits) of one or more chemically inactivated cell-culture-derived preparations of a seed virus strain blended with a suitable adjuvant/s and excipients. **Antigen banks** may be defined as stockpiles of antigen components, registered or licensed according to the finished vaccine, and which can be stored under ultra-low temperatures for a very long time for subsequent formulation into vaccine as and when required.

FMD vaccines may be classified as either 'standard' or 'higher' potency vaccines. **Standard potency** vaccines are formulated to contain sufficient antigen and appropriate adjuvant to ensure that they meet the minimum potency level required (recommended as 3 PD50 [50% protective dose]) for the duration of the shelf life claimed by the manufacturer. This kind of vaccine is usually suitable for use in routine vaccination campaigns. For vaccination in naïve populations to control FMD outbreaks, **higher potency** vaccines (e.g.> 6 PD50 for the duration of the shelf life claimed by the manufacturer) are recommended for their wider spectrum of immunity as well as their rapid onset of protection.

Conventional live attenuated vaccine types for FMD are not acceptable due to the danger of reversion to virulence and their use would prevent the detection of infection in vaccinated animals.

FMD vaccines can be monovalent or polyvalent in relation to the serotype of antigen. Because of the presence of multiple serotypes of the virus, it is common practice to prepare vaccines from two or more different virus serotypes. In certain areas, it may be advisable to include more than one virus strain per serotype to ensure broad antigenic coverage against prevailing viruses.

Currently, a number of commercially manufactured vaccines are available of differing strain composition, antigenic content, adjuvant formulation and cost. All are produced using inactivated antigens. Vaccine is available as fully formulated and tested product or, more usually in emergency situations, it can be freshly formulated from concentrated, inactivated antigen(s) stored at low temperature in vaccine banks maintained by commercial manufacturers or by national and international authorities. Inactivated FMD vaccines are unable to induce sterile immunity, and viral replication may happen in the epithelial surface of vaccinated animals, resulting in a carrier state of FMDV [8]. Although no evidence showed that the vaccinated carrier cattle could transmit the virus.

The FMD vaccines available from commercial sources have remained virtually unchanged for several decades and there has been less investment in research and development by manufacturers than was formerly the case. FMD vaccine is a high-cost product in particular since it must be produced within biosecure facilities which are expensive to establish and maintain, particularly in developing countries.

Method of manufacture – OIE Terrestrial Manual

The recommended method of virus propagation for antigen production is the growth of FMDV in large-scale suspension cultures or monolayers of an established cell line (BHK). When the virus is expected to reach the maximum yield, the culture is clarified, and the virus is subsequently inactivated by addition of an inactivant usually binary ethyleneimine (BEI). After inactivation, any residual BEI can be removed or neutralized. The inactivated virus may be concentrated/purified by procedures such as ultrafiltration, polyethylene glycol precipitation or polyethylene oxide adsorption. Concentrated inactivated virus may be purified further by procedures such as chromatography. These concentrated antigens can be formulated into vaccines or stored at low temperatures for many years.

Conventional FMD vaccines are usually formulated as oil adjuvanted or aqueous vaccines. Oil-adjuvanted vaccines are usually formulated as water-in-oil emulsion. Double emulsions may also be used. The aqueous vaccine is prepared by adsorbing the virus on to aluminium hydroxide gel. The final blend of the vaccine may include other components such as antifoam, phenol red dye, lactalbumin hydrolysate, tryptose phosphate broth, amino acids, vitamins, buffers, salts and other substances. An adjuvant, such as saponins, and preservatives may also be incorporated.

For vaccines destined for cattle, both aluminium hydroxide saponin adjuvanted and oil adjuvanted vaccines are used. Oil adjuvanted vaccines are at least as effective as aluminum hydroxide vaccines in ruminants, but whether they induce better immunity has been debated. Double oil-emulsion vaccines are thought to provide a stronger and longer antibody response than water-in-oil single emulsion vaccines. Vaccines with oil adjuvants are reported to have a better shelf life. The aluminum hydroxide-saponin formulated vaccines have the advantage of being easier to produce, however they can cause granulomas at the inoculation site and are not effective in pigs [9]. For use in swine, double oil emulsions are preferred due to their efficacy. Aluminum hydroxide vaccines are also less potent per microgram of antigen, and produce a shorter duration of immunity [10].

The shelf life of conventional formulated FMD vaccines is usually 1-2 years at 4°C (range 2-8°C). Some emergency FMD vaccines may be less stable. This effect has been reported for some vaccines but not for others, and might be caused by proteases from the culture harvest and/or the type of formulation [1].

Strain-related differences may affect vaccine manufacture and storage. When used in a vaccine, serotype O is less immunogenic than other serotypes, and requires a higher antigen payload. The payload of each antigen generally varies from 1 to 10 µg, depending on the antigenicity of the strain. In case of serotype O and SATs,

more antigen is required compared with serotype A, Asia I and C, in order to achieve an equivalent potency. This type of variation in potency may be attributed to the unequal stability of antigen in different serotypes of FMDV. The 146S particles have been considered as an immunogenic component of FMD vaccines and any degradation of 146S particles may reduce the potency of the vaccine [11]. SAT-1, SAT-2, and SAT-3 viruses are less stable than other serotypes, and SAT-2 and SAT-3 viruses can dissociate under mildly acid conditions. FMDV capsids comprise twelve-pentameric protein assemblies held together by tenuous electrostatic and hydrophobic interactions. Disassembly and the release of the RNA genome can be triggered by pH <7 or temperature >30°C. The serotypes with a highly significant impact in East Africa e.g. O and SAT2, are least stable, and current vaccines, produced by chemical inactivation of live virus, further destabilize the capsid. Capsid integrity is essential since the presentation of multiple copies of epitopes elicits protective immune responses**.** To ensure that vaccines containing the SAT serotypes are potent and remain so during storage, extra quality assurance steps must be taken. Controls for FMD vaccines, can be seen in Figure 16.

Vaccine matching tests

Appropriate vaccine strain selection is an important element in the control of FMD (Figure 16). Vaccination against one serotype of FMDV does not cross-protect against other serotypes and may also fail to protect fully or at all against other strains of the same serotype. The two important determinants that will affect the efficacy of a vaccine and determine whether it will protect or not are:

1) the ability of the vaccine strain to elicit antibodies that will cross-react and protect against the field or outbreak virus in question (defined as the vaccine or antigenic match), and

2) the potency of the vaccine to elicit a strong and long-lasting immune response. Higher potency vaccines result in a faster onset of immunity and less virus shedding. They are also thought to provide better protection against heterologous strains of FMDV within the same serotype, although this might vary with the strain. Boosters are an alternative to increase vaccine efficacy, and can also improve the breadth of antigenic cover by increasing the amount of cross-reactive antibodies. However, immunity develops more slowly than if a single dose of a highly potent vaccine is used, and protection against heterologous strains is not expected to last as long as with a well-matched vaccine. The quality and quantity of the antigen in the vaccine as well as the formulation of the vaccines and inclusion of immune-stimulating adjuvants are all factors that will influence and contribute to the overall potency of the vaccine. Formulating vaccines with higher potency may result in fewer doses if the antigen amount is limited, and it may be more expensive.

The most direct and reliable method to measure cross-protection is to vaccinate relevant target species and then to challenge them by exposure to the virus isolate against which protection is required. This will take account of both potency and cross-reactivity. However, such an approach requires the use of live FMDV and appropriate biosecurity procedures and practices must be used. This procedure is slow and expensive and requires specific expertise that is best available in OIE Reference laboratories. The use of animals for such studies should be avoided where possible by the use of in vitro alternatives.

A variety of *in vitro* serological methods can be used to quantify antigenic differences between FMDV strains and thereby estimate the likely cross-protection between a vaccine strain and a field isolate. Genetic characterization and antigenic profiling can also reveal the emergence of new strains for which vaccine matching may be required and, conversely, may indicate that an isolate is similar to one for which vaccine matching information is already available.

The OIE recommends that the two dimensional virus neutralization test (VNT) be used. Matching by ELISA has also been described; however, the OIE currently recommends its use only for screening. The 'r' value indicates the closeness of the match in serological tests, with r1 > 0.3 in the VNT suggesting that a potent vaccine is likely to be protective. Matching by serological tests cannot account for differences in vaccine potency. If r1 suggests that a vaccine strain does not provide a sufficient match for the field virus, a heterologous cross-protection challenge test can be conducted. Alternatives are to match the field isolate against other vaccine strains, or adapt a field virus to produce a new vaccine.

However, interpretation of the VNT is plagued by limitations, including the uncertainty as to how well the in vitro matching data actually correlates to in vivo cross-protection, the impact of vaccine potency on protection, and the availability of reference reagents. Furthermore, the use of r1-values to estimate cross-protection relies on having sufficient repeated measures to overcome the inherent variability of the neutralization titers [7]. In a recent study with SAT1 viruses, it was found that a number of factors impair reproducibility in one-way relationships, such as the operator, batch variability of reagents, day-to-day variation in the cells, and variation in individual cattle sera. It is also known that measuring the titer ratio to a known control is not sufficient to eliminate the inter-experiment variability, highlighting the necessity for time-consuming duplicate tests to be undertaken on separate and independent occasions to compensate for day-to-day variations. A novel way to quantify and visualize antigenic relationships is antigenic cartography. However, the combination of genetic sequencing and antigenic profiling of the outbreak virus are still useful methods to identify newly emerging or re-emerging virus strains and whether available vaccine strains are likely to provide protection against the outbreak virus or not. Alternatively, serological cross-reactivity can be estimated using a liquid-phase blocking ELISA, and more recently a new approach using linear mixed-effect models to estimate antigenic matching has also been described [7]. Simple antibody recognition measures do not always correctly predict the ability of a vaccine to protect against an outbreak virus. The antibody isotype, the avidity of the antibody to the virus in question, and the type of immune response elicited are also important factors to consider. In a recent study comparing the accuracy of traditional and novel serological assays to predict cross-protection, it was found that the use of VNT titers and r1-values are inaccurate indicators of protection. However, when the VNT titers were combined with the IgG1 titer, a more accurate estimate of FMD vaccine protection against the heterologous virus for serotype A was achieved. To date, the correlation of in-parallel serological data, like VNT and IgG1, IgG1/IgG2, or antibody avidity in cross-protection in the case of SAT viruses is unknown [7].

INTA in Argentina, developed and successfully evaluated two high-throughput ELISA techniques, avidity and IgG subtype ELISA to indirectly assess heterologous protection [12]. In later studies [13], when using traditional and novel serology tests, they concluded that due to the sensitivity of individual tests, two or more tests should be used in combination to produce an accurate estimation of protection. INTA has developed now a single dilution avidity ELISA for buffaloes' serum, that matches VNT results more accurately than LPB-ELISA which hasn't been launched yet (see Section 7, Note 4).

Basic capability to undertake vaccine matching tests on a routine basis in diagnostic laboratories in African countries is severely limited, and therefore current advice regarding the selection of the best vaccine to be used in these settings is normally provided by regional (ARC-Onderstepoort Veterinary Institute, South Africa; Botswana Veterinary Institute, Botswana) and international reference centers. The OIE/FAO FMD Reference Laboratory Network reports over the last five years have revealed a gap in the vaccine strains available to match against circulating SAT1 and especially SAT2 viruses. The urgent requirement for the development of new SAT vaccine strains with good immunogenicity for use in Africa was also highlighted at the recent Global FMD Research Alliance congress (Arusha, Tanzania in October 2013). For the African continent (FMD endemic pools 4, 5, and 6), at least five vaccine strains are available for SAT1, and seven vaccine strains are described for SAT2 viruses. However, not all these vaccine strains are of recent derivation or are currently used in production, and it is therefore imperative that outbreak samples are properly matched to the vaccine strains that are available for use in control programs [7].

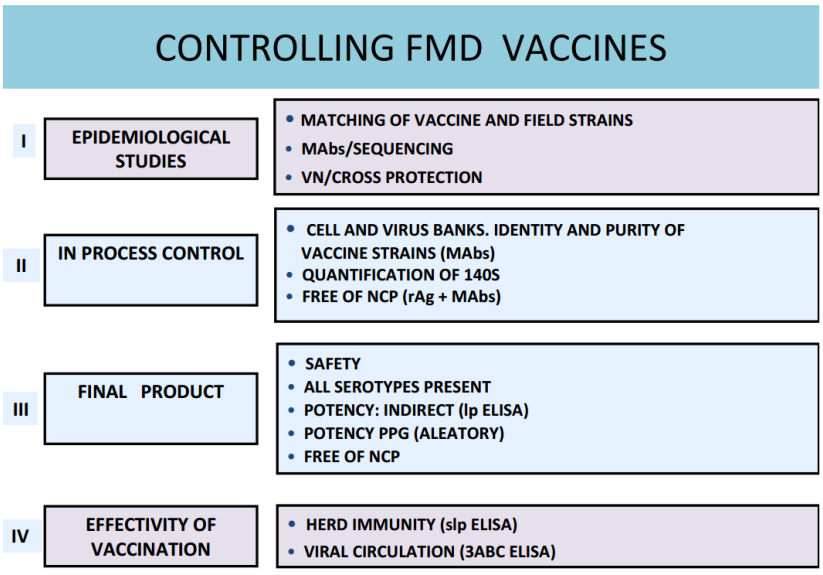


Figure 16: Controlling FMD vaccines. Source: Capozzo, 2012. Indirect parameters related to vaccine efficacy along the FMD vaccine production process. GFRA meeting, 2012.
http://www.ars.usda.gov/GFRA/presentations/Session8/8.3%20GFRA%202012_FINAL%20capozzo%20et%20al.pdf

Vaccine from outbreak strain

If a new vaccine must be prepared from an outbreak strain (either because no reasonably well-matched vaccine strain is available, or to optimize vaccine efficacy), the field virus must first be adapted to culture and suspension culture to produce enough antigen. While many new vaccines have been produced successfully, some field strains do not grow well in culture, and the quality or number of field strains from an outbreak might be inadequate. In addition, the adaptation process is time-consuming, and has the potential to result in antigenic changes during adaptation and in vitro growth.

An experimental approach, which might mitigate some of these difficulties, involves the development of new vaccine strains by modifying cDNA clones of existing strains. In a study published in 2013, a vaccine was developed for a serotype A virus that does not grow well in culture, by substituting the FMDV capsid coding region into the cDNA clone of a serotype O vaccine strain [14]. In a similar experiment, partial replacements of genetic material were made between field and vaccine strains of SAT viruses [15] . Another group reported making genetic modifications to an infectious cDNA clone of a serotype O vaccine strain, to provide broader protection against three related field viruses [16]. If the adaptation of a field strain to culture is successful, the lead time for vaccine preparation is 1 to 6 months, depending on how readily the strain grows in vitro, its yield and immunogenicity, and the tests that must be conducted.

Vaccines for SAT types for use in Africa

SAT vaccines are a particular case. Vaccination in Africa is complicated by the fact that not only are the 3 SAT serotypes of FMDV prevalent in most southern African buffalo populations, but also by considerable geographically-specific intratypic variation (topotypes) among these viruses (Annex 1). The SAT1 and SAT2 viruses display greater antigenic variation compared with the Euro-Asian serotypes. The consequence of this genetic variation is for example, that a SAT2 vaccine produced from a South Africa virus isolate will not necessary provide protection against a SAT2 outbreak in Kenya and certainly not a SAT2 outbreak in West Africa although it is able to elicit protective immune responses against the local circulating viruses. The diversity of circulating field strains makes the selection of sufficiently cross-protective FMD vaccine a challenge as already discussed. Local and regional programs of surveillance to monitor FMDVs circulating in wildlife and livestock are a crucial component of vaccine control, to provide vaccine matching data and access to appropriate viral strains.

On the other hand, vaccines for SAT types present their own difficulties. It has also been mentioned that SAT1, SAT2 and SAT3 viruses are less stable than other serotypes, and SAT2 and SAT3 can dissociate under mildly acidic conditions. The SAT vaccines need greater payload. Studies have been conducted to evaluate different adjuvants for SAT vaccines, and a double water-in-oil-in-water adjuvant, ISA206, elicited protective antibody responses against SAT2 serotype in cattle. Inactivated vaccines induce short-lived immunity, and it is recommended that naïve animals receive two initial vaccinations (a primary and secondary dose) 3–4 weeks apart, followed by re-vaccination every 4–6 months to prevent spread of disease within populations. However, in the African environment, this may differ for different manufacturers, depending on the potency of the

vaccine, and some manufacturers recommend five vaccinations per annum. There is a definite need to assess whether different adjuvants may enhance the duration of immunity against SAT antigens. For these reasons vaccination campaigns should be performed regularly, based on 1) the epidemiological circumstances and risk of disease spread, 2) the value and life expectancy of species, and 3) the economic status of the country. The interval between vaccinations is critical to prevent a "window of susceptibility" and where the continuous or sporadic presence of virus in carrier animals is present [7].

For more on vaccines for SAT types, please see Note 5 on Section 7, and also Section 8.

Recent developments – new licensed vaccines:

1. Replication defective hAd5-vectored FMD vaccine:

A human adenovirus 5-vectored serotype A24 FMD vaccines has received a conditional license in the USA, but is not being manufactured at this time [1]. This vaccine can be produced without the need for high biosecurity conditions, and is compatible with DIVA testing. It is made as a ready-to-use vaccine, and initial estimates suggest that it can be stored frozen for at least 3 years. Vectors generated from human adenovirus 5 (hAd5), a mild respiratory pathogen of people, use the replication-defective hAd5, a live vector that lacks three regions of the adenovirus genome necessary for virus replication. As a result, it cannot produce new adenoviruses except in vitro, within cell lines that have been engineered to contain certain complementation functions. When a vaccine construct is transfected into such a packaging cell line, the cell generates virus-like particles consisting of the DNA vector inside an adenovirus capsid. These particles are able to attach to the cells of a number of animal species and become internalized; however, they cannot replicate and infect additional cells. Once the virus particle enters the cell, the vaccine construct is transported to the nucleus and transcribed. The hAd5-vectored FMD vaccine construct encodes all of the FMDV capsid proteins, as well as a few NSPs (2A, 3C and sometimes 2B) necessary to generate these proteins from the viral precursor polyprotein. The result is the expression of FMDV capsid proteins in the animal, and their assembly into "empty capsids," which do not contain infectious nucleic acids. The hAd5 vector does not integrate into the host genome, and the expression of vaccine proteins is transient.

Some completed steps include production and characterization of a master seed virus, master cell line production and characterization, the establishment of a scalable manufacturing process for vaccine production, technology transfer to a USDA-licensed manufacturing facility and the receipt of regulatory approval for an outline of production. The company is also developing hAd5-vectored FMD vaccines for other serotypes and strains, to follow conditional and full USDA licensing programs. An entire program for the licensure of 10 separate single master seeds expressing relevant FMD constructs is under consideration as a 5-6 year program.

Most research has been conducted with a construct for A_{24} Cruzeiro. New vaccines can be generated in this system by replacing the capsid coding sequence in the hAd5 vaccine construct. Theoretically, this could produce

effective vaccines for a variety of FMDV serotypes and strains, including field strains that have not been adapted to cell culture. In practice, some of these constructs might be less effective than the A_{24} Cruzeiro vaccine, at least using the original vector. Early experiments with serotype O vaccines (which require higher antigen doses in conventional vaccines) did not demonstrate sufficient protection in pigs. An hAd5-vectored O1 Campos vaccine provided only partial protection from challenge. Furthermore, pigs vaccinated with a bivalent vaccine (A_{24} Cruzeiro and O1 Campos) produced neutralizing antibodies against both serotypes, but the antibody titers were much lower than titers induced by either conventional commercial FMD vaccines or a monovalent hAd5-A24 Cruzeiro vaccine in previous experiments.

Some concerns about the use of this vaccine, include that immune responses to the adenovirus vector might limit the vaccine's efficacy if there is pre-existing immunity to other hAd5-vectored vaccines, or if multiple doses must be given. Several studies have detected antibodies to this vector in cattle and pigs immunized with hAd5-vectored FMD vaccines. An experiment in pigs indicated that pre-existing immunity might be a concern, when the vaccine was given 2 weeks after injecting the vector alone. In cattle, titers to the vector tend to peak 2 weeks after vaccination, and a second dose ofhAd5-vectored FMD vaccine, given after the titers had declined, was able to boost the immune response. Other concerns include the need for a relatively high dose to induce protection, and the cost of the vaccine. However, recent studies have shown that a SC vaccine in the neck could reduce the dose, and the adjuvant poly-L-lysine and carboxymethyl cellulose (ICLC) reduced the vaccine dose [17].

2. Commercial FMD synthetic-peptide vaccine:

Commercial FMD synthetic-peptide vaccines for use in pigs are available in Asia, but little information is available, and surprisingly, there are not many references in the literature. As far as we could find, there are 3 of this type of vaccine licenced in China. From Tiankang Biopharmaceutical (licensed in 2010), China animal husbandry group (licensed in 2014), and UBI (licensed in 2014). The first two are based on peptides 2570 + 7309, while the UBI vaccine is based on peptides 2600 + 2700 + 2800.

The FMD synthetic-peptide vaccine from UBI for the prevention of pig FMD was developed by UBI Company and licensed for use in Taiwan (www.unitedbiomedical.com) and mainland China (since 2007). The peptide vaccine is based on a sequence from the prominent G-H loop of VP1, one of the 4 capsid proteins. The sequence was optimized by the inclusion of a cyclic constraint and adjoining sequences, and broader immunogenicity was obtained by the incorporation of consensus residues at hypervariable positions. The peptide also included a promiscuous T-helper epitope for effective immunogenicity in outbred populations of large animals [18]. The composition of the peptide should undertake adjustment according to the pandemic strains of FMDV, when the amino acid in the G–H loop domain of a vaccine does not match with circulating FMDV isolate would lead to FMD outbreak. According to UBI, over a billion doses have been sold of the swine vaccine. The advantages of the UBI vaccine, as claimed by the manufacturer, can be seen in Table 11:

http://www.unitedbiomedical.com/animal-health-vaccines.htm, **http://www.unitedbiomedical.com/Foot-and-mouth-vaccine.htm**.

In pigs, peptide/protein vaccine candidates have been shown to be promising. Unfortunately, these positive results in pigs have not been consistently observed in cattle. Also, UBI peptide vaccine tested in cattle showed that this vaccine induced low levels of anti-FMDV serum neutralizing antibodies and failed to protect cattle against FMDV type O challenge. It is not allowed to be used in cattle in China [17].

Table 11: Advantages of the UBITh® FMD synthetic-peptide vaccine. Source: UBI

Disadvantages associated with current FMD vaccines	Key advantages of UBITh® FMD vaccines over classical vaccines
• The virus must be produced in a high containment facility to prevent contamination of the immediate environment • The handling of the virus also means the imposition of restrictions on the movement of the personnel involved • The innocuity of the product must be ensured. Several cases of the disease have been traced to improperly inactivated virus. • The product must be inspected at regular intervals to insure immune-potency. In some countries this can be as frequent as 3 times each year. • The product must be reformulated regularly with current field strains to prevent loss of protective efficacy against newly evolved antigenic variants. • Adverse side effects	• A single procedure for the rapid production and validation of vaccine for newly emerging strains • Consensus sequence for breadth of cross-protection wider than the killed vaccines • Combinatorial UBITH® sequence for coverage of all animals in genetically diverse populations • Defined antigenic marker vaccine, for clear-cut distinction of vaccinated from unvaccinated animals (VP1 tests) and clear differentiation of vaccinated from convalescent animals (NS tests). • Absolute safety from biohazard risk, both during manufacture and use • No toxicity or side effects • Low manufacturing costs

According to UBI website, UBI export their FMD vaccines mainly to China, where they have 35% of the market share. There are 2 subsidiaries in China. The one called UBI Shanghai (Shen Lian Biotechnology Co, Ltd) has an annual production of over 800 million doses.

Technical information:

- Active ingredients: The vaccine contains at least 25mcg/ml peptides 2600+2700+2800
- Dose: 1 ml.
- Route: IM (in the neck)
- Primary vaccination: 2 vaccinations, 4 weeks apart.
- Booster: every 6 months. Repeat every 4-6 months.
- Presentation: 50 and 100 ml vials.
- Conservation & shelf life: Between 2 – 8°C for 12 months.
- Side effects: Some pigs might have fever for several days after vaccination (less than with inactivated vaccines)
- No information available on efficacy, age and onset of immunity

The vaccines from Tiankang Biopharmaceutical and China animal husbandry group have similar characteristics, except for the use of different peptides.

Personal communications from private pig practitioners in China, have informed that they evaluated the vaccine 3 years ago, and the level of antibodies was very good, however the protection from clinical signs was poor as compared with the inactivated vaccines.

Vaccine Banks

Non-commercial FMD vaccine banks, which can be activated in emergencies, are maintained in some individual countries. There are also two multinational cooperative banks: the North American Vaccine Bank (NAFMDVB) for the United States, Canada and Mexico, and the European Union Vaccine Bank (EUVB) for the E.U. Non-commercial vaccine banks usually operate on a relatively small scale, and an individual bank may be able to meet only the initial needs during an outbreak. Because some stocks are duplicated in different banks, it might be possible to obtain additional vaccine supplies from other countries. In 2006, representatives of FMD vaccine banks approved the creation of an international FMD vaccine bank network, to operate under the auspices of the OIE. Some of the goals of the network include addressing sudden increases in the demand for vaccine and establishing a global vaccine reserve for FMD, as well as harmonizing vaccine and test standardization and certification.

FMD vaccine banks usually store concentrated antigens, which can be kept at ultra-low temperatures for many years. In an outbreak, banks can rapidly formulate stored antigens into complete vaccines. Banks are usually

able to make either monovalent or polyvalent vaccines that contain oil or aluminum hydroxide/ saponin as the adjuvant. It is possible to adjust the potency of the vaccine according to need and to the relatedness of the field and vaccine strains. The time between receipt of the order and vaccine delivery has been estimated to be 4 to 13 days, depending on the distance the antigens and/or vaccine must be shipped, the daily finishing and filling capacity of the manufacturer and the availability of flights. Vaccine banks can store only a limited number of serotypes and strains. Vaccine strains held in banks are generally those felt to have the greatest risk of introduction, based on the worldwide epidemiological situation. These stocks are under continual review.

Immunity

Inactivated FMD vaccines are thought to protect animals by inducing humoral immunity, although there is some evidence that they may also stimulate some degree of CMI possibly as the result of cross-priming. Inactivated FMD vaccines are not thought to result in any mucosal immunity with the possible exception of certain highly potent vaccines, given repeatedly [1]. It also appears that animals vaccinated with FMDV do not elicit a predominant antibody response against a single antigenic site, but rather utilize a broad repertoire of epitopes on the viral capsid [7].

Main vaccine needs

There is a need for a vaccine that:

1- Provides sterile immunity

2- Has DIVA capabilities

3- Uses technology that makes easier to match field strains with vaccine strain

4- Does not required high level of biosecurity for production

Commercial vaccines manufactured in Africa and Asia

The information summarized in Table 12 below, is based on information from The Center for Food Security and Public health, Iowa State University (**www.cfsph.iastate.edu/vaccines/index.php** and Vetvac (**www.vetvac.org**). More details have not been gathered, as another consultant has been commissioned to perform this task.

Table 12: Manufacturers of FMD vaccines in Asia and Africa.

Manufacturer	Country	Name & Strain	Vaccine Type / Adjuvant	Countries distribution
ASIA				
Tiankang Biopharmacuetical	China	FMD Type O Inactivated OS 99	Killed	
		FMD Type O Inactivated (II) OZK93	Killed	
		FMD Type O Inactivated OS99 + OZK93		
		FMD Type O Synthetic Peptide Peptides 2570 + 7309		
		FMD Type O Inactivated Type O		
		FMD Type O, Asia 1 Bivalent OHMO2 + Asia 1		
China Animal Husbandry Group	China	FMD (Type O) Vaccine, OS/99 Strain	Killed. Double oil adjuvant Montanide 206	
		FMD type O vaccine OS/99 strains	Killed	
Biovet Private Limited	India	BioFMD-Oil™ O, A, Asia-1	Killed Oil	
Brilliant Bio Pharma Ltd.	India	FUTVAC™ O, A, Asia-1	Killed Oil	
Indian Immunologicals Limited	India	Raksha Triovac (FMD, Hemorrhagic Septicemia, Blackleg Disease)	Killed Oil	

		O, A, Asia-1		
		Raksha Biovac (FMD, Hemorrhagic Septicemia) O, A, Asia-1	Killed Oil	
		Raksha Ovac O, A, Asia-1	Killed Oil	
		Raksha O, A, Asia-1	Killed Aluminum hydroxide, saponin	
Brilliant Bio Pharma Ltd.	India	FUTVAC (FMD Vaccine, Inactivated IP) 'O' (strain IND R2/75), 'A' (strain IND 40/2000) and 'Asia1' (strain IND63/72)	Killed. Mineral oil (ISA Montanide 206 from Seppic)	
Merial Philippines	Philippines	Aftopor Monovalent O1 Philippines	Killed Oil	
		Aftopor Trivalent A24 Cruzeiro, C3 Philippines, O1 Philippines	Killed Oil	
FMD Center	Thailand	FMD Vaccine for Pigs O, A, Asia-1	Killed Oil	
		FMD for Cattle, Sheep, Goats O, A, Asia-1	Killed Aqueous	
MSD		Decivac FMD DOE O1 Manisa	Killed, Double oil emulsion	Algeria, Philippines
AFRICA				
Botswana Vaccine Institute	Botswana	AFTOVAX® O, A, SAT-1, SAT-2, SAT-3	Killed Aluminum hydroxide, saponin	Botswana, Eritrea, Malawi, Mali, Mozambique, Namibia, Nigeria, Senegal, South

				Africa, Zambia, Zimbabwe
Middle East Veterinary Vaccine (ME VAC)	Egypt	Tri-Aphthovac A Iran 05, O panAsia-2, SAT-2	Killed Montonide ISA-50	
Veterinary Serum and Vaccine Research Institute	Egypt	Monovalent Inactivated FMD Vaccine O1 93	Killed Aluminum hydroxide	
		Bivalent Inactivated FMD Vaccine O1 93, AEGY/06	Killed Aluminum hydroxide	
		Polyvalent Inactivated FMD Oil Vaccine O, A, SAT2	Killed Oil	
National Veterinary Institute of Ethiopia	Ethiopia	FMD Vaccine A and O serotype	Killed. Absorbed on aluminium hydroxide gel and adjuvanted with saponin.	
Kenya Veterinary Vaccines Institute-KEVEVAPI	Kenya	FOTIVAX O, A, C, SAT 1, SAT2	Killed. Aluminium hydroxide gel. Saponin	Kenya, Rwanda, Sudan, Tanzania, Uganda

FMD Manufacturers in China (2011). Source: **Qiang & Huachun**. FMD vaccines and vaccination in China, production use and quality. International conference on scientific developments and technical challenges in the progressive control of FMD in South Asia. New Delhi, 2011.

Producers	Vaccine	Producer located
China Agricultural Vet. Bio. Science and Technology Co., Ltd	All types	Gansu
Lanzhou Biological Pharmaceutical of China Animal Husbandry Industry Co., Ltd	O,Asia1 inactivated	Gansu
The Spirit Jinyu Biological Pharmaceutical Co., Ltd	O,Asia1 inactivated	Inner-Magnolia
BWAT Bio. Science and Technology Co., Ltd	O,Asia1 inactivated	Inner-Magnolia
Xinjiang Tecon Animal Husbandry Bio-technology Co., Ltd. (Tecon)	O,Asia1 inactivated	Xinjiang
QYH Biotech Company Limited	O,Asia1 inactivated	Yunnan
Shenlian Biotech Co., Ltd	Synthetic peptide	Shanghai

Commercial vaccines imported into Africa and Asia

The information summarized in Table 13 is based on the questionnaire sent to the Directors of Veterinary Services office and regulators of the countries of interest. Note that some vaccines might have been imported under DVS dispensation, and they are not necessary licensed in the country.

Table 13: Commercial FMD vaccines imported into the countries of interest

Country	Vaccine name	Strain or type	Country of origin	Doses imported 2015	Doses imported 2014	Doses imported 2013	Doses imported 2012
ASIA							
Bangladesh	Aftovaxpur (Merial)	O, A & Asia-1	UK	395,000	350,000	400,000	450,000

	Raksha (IIL)	O & A	India	111,000	120,000	95,000	175,000
India							
Indonesia							
Myanmar (Burma)	Af to por OA Asia1	O, A & Asia-1	France[1]	-	100	9,000	3,000
Nepal	-	-	-	-	-	-	-
Vietnam[2]					16,571,720	20,033,500	23,364,440
AFRICA							
Burkina Faso							
Côte d'Ivoire (Ivory Coast)	-	-	-	-	-	-	-
Ethiopia							
Kenya	-	-	-	-	-	-	-
Madagascar							
Malawi	Trivalent FMD	SAT 1, 2 & 3	Botswana	10,000	30,000	15,000	-
Mali	Aftovax	SAT1, A & O	Botswana	9,000	31,200	15,000	-
Mozambique							
Rwanda	Fotivax	A, O, SAT1, SAT2	Kenya	70,000	80,000	100,000	120,000
Senegal							
South Africa							
Tanzania	-	-	-	-	-	-	-

Uganda[3]	Fotivax	O, SAT1, SAT2	Kenya	980,000	400,000	300,000	476,000
Uganda[4]	Fotivax	O, SAT1, SAT2	Kenya	730,000	683,200	337,000	150,000 (est)
	Aftovax		Botswana	150,000			
Zambia	-	-	-	-	-	-	-

- Questionnaire received, no information provided.

1: There are no FMD vaccine manufacturers in France, so this is probably a mistake. Based on the name of the vaccine given is not possible to be sure, but it might be the vaccine from Merial.
2: Companies with FMD vaccines registered to import into Vietnam (as supplied by the DVS) are: Intervet (Devivac), Zoetis, Merial, Lanzhou Veterinary Research Institute, Harbin, China Agricultural Veterinary Biological Science and Technology.
3: Reply from the National Drug Authority, Uganda.
4: Reply from the Veterinary services office, Uganda.

Combination vaccines

Current use: The only commercial FMD combination available, is Raksha Biovac, a combination of FMD and Haemorrhagic septicaemia, produced by India Immunologicals Limited (IIL).

Desirable combinations:

- Cattle: Depending on the geography to be used.
- Small ruminants: Depending on the geography to be used.
- Pigs: for a vaccine targeted to Asia, the combination with porcine cysticercosis might be a very good opportunity to transform a public good (cysticercosis), into private good. Combination with other vaccines like CSF and PPRS might also be of interest for Asia.

Characteristics of Ideal Vaccine Candidates for Smallholders

The Target Product Profiles (TPPs) reflect the availability and utility of current agents and incorporate features that will be necessary to improve on the current products and to address unmet needs, taking into account the particular requirements of the poorest livestock keepers.

The TPPs are more robust when they include the opinions and consider the needs of the different stakeholders. While efforts have been made to encompass them, the TPP showed in Table 14 below, should be considered a proposal, a live document subject to improvements.

Important note: The TPP might be different, depending on the purpose of the vaccine. For example, slightly different TPPs might be needed for a vaccine for an endemic area, a vaccine for eradication, or a vaccine for emergency situations.

Minimum attributes (current available vaccine) is based on the following information:

Aftovaxpur SPC:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/002292/WC500147985.pdf (double oil emulsion)

Fotivax (Kevevapi): **http://www.kevevapi.org/index.php/products/item/15-fotivax-tm** (Aluminium hydroxide and saponin)

FMD Vaccine (NVI): **http://www.nvi.com.et/fmd.html** (Aluminium hydroxide gel and saponin)

Ideal and current attributes have also been included as described in Rodriguez & Gay, 2011 [10].

Table 14: Target Product Profile (TPP) FMD – Proposal:

	Attribute	Minimum (current available vaccine)	Ideal
1	Antigen	Inactivated FMD virus (varying number of strains)	Immunogen with protective antigens for FMDV
2	Indication for use	Active immunization of cattle and sheep from 2 months of age and pigs from 10 weeks of age against FMD to reduce clinical signs. Some manufacturers say cattle over 6 months of age. NVI recommends in Ethiopia to vaccinate cattle before November and January (high risk season)	For active immunization of cattle, buffalo, sheep, goats, pigs, and wildlife to prevent infection and transmission
3	Recommended species	Cattle, sheep, goats and pigs	Cattle, buffalo, sheep, goats and pigs. Also all susceptible animals, including susceptible wildlife.
4	Recommended dose	Standard vaccines: $3PD_{50}$ High potency vaccines: ≥ 6 PD_{50} Cattle from 2 months of age: 2 ml Sheep from 2 months of age: 2 ml Pigs from 10 weeks of age: 2 ml Some manufacturers indicate 3 ml for cattle, but 2 for small ruminants and pigs. Other manufacturers recommend 4 ml for cattle.	Same dose for all species (1 or 2 ml)
5	Pharmaceutical form	Oil: Emulsion for injection (white emulsion after shaking)	Ready to use solution/suspension
6	Route of administration	Ruminants: SC Pigs: IM	SC or IM (oral might be important for wild buffaloes)

7	Regimen - primary vaccination	One injection	Single lifetime dose
8	Regimen - booster	Every 6 months. Some manufacturers recommend 4 months.	Lifelong immunity after primary vaccination
9	Epidemiological relevance	Protection against disease	Protection against infection. Prevents development of carrier state.
10	Recommended age at first vaccination	If used in an emergency situation requiring mass vaccination, limited data suggests that the vaccine can be safely administered to cattle and pigs from 3 weeks of age	From 1-2 months of age, when other vaccines are applied.
11	Onset of immunity	7 days – 4 weeks (vaccines with high payload, can induce partial protection at 4 days post vaccination)	1 day
12	Duration of immunity	4-12 months (Depending on vaccine formulation and species).	Lifelong immunity
13	Expected efficacy	Reduction of disease severity and clinical signs. Does not prevent infection.	To prevent infection n and transmission in 100% of the animals. No disease after virulent challenge.
14	Expected safety	Oil adjuvant: May produce swellings (diameter of up to 12 cm) in most animals. Normally resolves over 4 weeks, but may persist for longer in a small number of animals. It is common to observe a slight increase of rectal temperature of up to 0.7 °C for 4 days postvaccination. AlOH: Swelling may occur at the place of inoculation and persist for a few weeks. Can be used during pregnancy.	No post-vaccinal reactions at any age. Safe for pregnant animals at any stage. Safe for all sexes at any age.

15	Withdrawal period	21-60 days Some manufacturers: 0 days.	Nil for milk and meat
16	Special requirements for animals	Vaccinate healthy animals only	Vaccinate all animals
17	Special requirements for persons	Precautions if self-injection with oil adjuvanted vaccine	None
18	Package size	50, 100 & 300 ml vials	Multiple pack size from 5 doses
19	Price to end user		
20	Storage condition and shelf-life as packaged for sale	2°C-8°C - 1 year. Varies depending on strains (some can be as short as 2 months).	Stable at 30°C for 4 years
21	In-use stability	Should be used immediately	24 hours or greater
22	Other: Cross-protection	Only within some serotypes	Across all 7 serotypes
23	Other: Requirement for high biosecurity containment	Yes, growth of large amounts of infectious virus	No, noninfectious or attenuated vaccines virus production platform.
24	Other: DIVA compatible	Requires antigen purification	Negative marker engineered into vaccine platform
25	Other: Ability to incorporate emerging viral strains	Requires adaptation of field strains	Allows rapid production of new antigens

Limitations

Scientific quality: The publications and data from the different research groups, should be carefully evaluated. The use of good science and good experimental design with use of proper controls, adequate numbers, suitable challenge model, reproduction of results by them and by independent groups, and appropriate analysis has not been verified for this monograph. If any of these projects were to be pursued, a detailed peer review taking into account the above considerations is strongly recommended.

References

[1] USDA and The Center for Food Security & Public Health. Iowa State University U. NAHEMS Guidelines: Vaccination for contagious diseases. Appendix A: Foot-and-mouth disease. FAD PReP Foreign Animal Disease Preparedness & Response Plan. NAHEMS National Animal Health Emergency Management System. 2015.

[2] Jamal SM and Belsham GJ. Foot-and-mouth disease: past, present and future. *Vet Res* 2013; **44**: 116.

[3] Couacy-Hymann E, Aplogan GL, Sangare O *et al.* [Retrospective study of foot and mouth disease in West Africa from 1970 to 2003]. *Rev Sci Tech* 2006; **25**: 1013-1024.

[4] Knight-Jones TJ and Rushton J. The economic impacts of foot and mouth disease - what are they, how big are they and where do they occur? *Prev Vet Med* 2013; **112**: 161-173.

[5] Govindaraj G, Ganeshkumar B, Nethrayini KR *et al.* Farm Community Impacts of Foot-and-Mouth Disease Outbreaks in Cattle and Buffaloes in Karnataka State, India. *Transbound Emerg Dis* 2015.

[6] Sinkala Y, Simuunza M, Pfeiffer DU *et al.* Challenges and economic implications in the control of foot and mouth disease in sub-saharan Africa: lessons from the zambian experience. *Vet Med Int* 2014; **2014**: 373921.

[7] Maree FF, Kasanga CJ, Scott KA *et al.* Challenges and prospects for the control of foot-and-mouth disease: an African perspective. *Veterinary Medicine: Research and Reports* 2014; **5**: 119-138.

[8] Alexandersen S, Zhang Z and Donaldson AI. Aspects of the persistence of foot-and-mouth disease virus in animals--the carrier problem. *Microbes Infect* 2002; **4**: 1099-1110.

[9] Ludi A and Rodriguez L. Novel approaches to foot-and-mouth disease vaccine development. *Dev Biol (Basel)* 2013; **135**: 107-116.

[10] Rodriguez LL and Gay CG. Development of vaccines toward the global control and eradication of foot-and-mouth disease. *Expert Rev Vaccines* 2011; **10**: 377-387.

[11] Parida S. Vaccination against foot-and-mouth disease virus: strategies and effectiveness. *Expert Rev Vaccines* 2009; **8**: 347-365.

[12] Lavoria MA, Di-Giacomo S, Bucafusco D, Franco-Mahecha OL, Perez-Filgueira DM and Capozzo AV. Avidity and subtyping of specific antibodies applied to the indirect assessment of heterologous protection against Foot-and-Mouth Disease Virus in cattle. *Vaccine* 2012; **30**: 6845-6850.

[13] Brito BP, Perez AM and Capozzo AV. Accuracy of traditional and novel serology tests for predicting cross-protection in foot-and-mouth disease vaccinated cattle. *Vaccine* 2014; **32**: 433-436.

[14] Zheng H, Guo J, Jin Y *et al.* Engineering foot-and-mouth disease viruses with improved growth properties for vaccine development. *PLoS One* 2013; **8**: e55228.

[15] Blignaut B, Visser N, Theron J, Rieder E and Maree FF. Custom-engineered chimeric foot-and-mouth disease vaccine elicits protective immune responses in pigs. *J Gen Virol* 2011; **92**: 849-859.

[16] Li P, Bai X, Sun P *et al.* Evaluation of a genetically modified foot-and-mouth disease virus vaccine candidate generated by reverse genetics. *BMC Vet Res* 2012; **8**: 57.

[17] Cao Y, Lu Z and Liu Z. Foot-and-mouth disease vaccines: progress and problems. *Expert Rev Vaccines* 2016: 1-7.

[18] Wang CY, Chang TY, Walfield AM *et al.* Synthetic peptide-based vaccine and diagnostic system for effective control of FMD. *Biologicals* 2001; **29**: 221-228.

[19] Kotecha A, Seago J, Scott K *et al.* Structure-based energetics of protein interfaces guides foot-and-mouth disease virus vaccine design. *Nat Struct Mol Biol* 2015; **22**: 788-794.

[20] Porta C, Kotecha A, Burman A *et al.* Rational engineering of recombinant picornavirus capsids to produce safe, protective vaccine antigen. *PLoS Pathog* 2013; **9**: e1003255.

[21] Reeve R, Blignaut B, Esterhuysen JJ *et al.* Sequence-based prediction for vaccine strain selection and identification of antigenic variability in foot-and-mouth disease virus. *PLoS Comput Biol* 2010; **6**: e1001027.

[22] Uddowla S, Hollister J, Pacheco JM, Rodriguez LL and Rieder E. A safe foot-and-mouth disease vaccine platform with two negative markers for differentiating infected from vaccinated animals. *J Virol* 2012; **86**: 11675-11685.

[23] Li P, Lu Z, Bai X *et al.* Evaluation of a 3A-truncated foot-and-mouth disease virus in pigs for its potential as a marker vaccine. *Vet Res* 2014; **45**: 51.

[24] Fowler VL, Bashiruddin JB, Maree FF *et al.* Foot-and-mouth disease marker vaccine: cattle protection with a partial VP1 G-H loop deleted virus antigen. *Vaccine* 2011; **29**: 8405-8411.

[25] Wang CY, Chang TY, Walfield AM *et al.* Effective synthetic peptide vaccine for foot-and-mouth disease in swine. *Vaccine* 2002; **20**: 2603-2610.

[26] Cubillos C, de la Torre BG, Jakab A *et al.* Enhanced mucosal immunoglobulin A response and solid protection against foot-and-mouth disease virus challenge induced by a novel dendrimeric peptide. *J Virol* 2008; **82**: 7223-7230.

[27] Shao JJ, Wong CK, Lin T *et al.* Promising multiple-epitope recombinant vaccine against foot-and-mouth disease virus type O in swine. *Clin Vaccine Immunol* 2011; **18**: 143-149.

[28] Guo HC, Sun SQ, Jin Y *et al.* Foot-and-mouth disease virus-like particles produced by a SUMO fusion protein system in Escherichia coli induce potent protective immune responses in guinea pigs, swine and cattle. *Vet Res* 2013; **44**: 48.

[29] Mohana Subramanian B, Madhanmohan M, Sriraman R *et al.* Development of foot-and-mouth disease virus (FMDV) serotype O virus-like-particles (VLPs) vaccine and evaluation of its potency. *Antiviral Res* 2012; **96**: 288-295.

[30] Pacheco JM, Brum MC, Moraes MP, Golde WT and Grubman MJ. Rapid protection of cattle from direct challenge with foot-and-mouth disease virus (FMDV) by a single inoculation with an adenovirus-vectored FMDV subunit vaccine. *Virology* 2005; **337**: 205-209.

[31] Yin C, Chen W, Hu Q *et al.* Induction of protective immune response against both PPRV and FMDV by a novel recombinant PPRV expressing FMDV VP1. *Vet Res* 2014; **45**: 62.

[32] Srinivasan VA, Reddy GS, Rao KA and Kihm U. Serological response of bovines to combined vaccine containing foot and mouth disease virus, rabies virus, Pasteurella multocida and Clostridium chauvoei antigens. *Veterinarski Arhiv* 2001; **71**: 37-45.

[33] Trotta M, Lahore J, Cardoso N *et al.* Simultaneous immunization of cattle with foot-and-mouth disease (FMD) and live anthrax vaccines do not interfere with FMD booster responses. *Trials in Vaccinology* 2015; **4**: 38-42.

Other resources used:

1. Infectious Diseases of Livestock. 2nd Edition. Edited by J A W Coetzer and R C Tustin. Oxford University Press Southern Africa. 2004.

2. NAHEMS Guidelines: Vaccination for contagious diseases. Appendix A: Foot-and-mouth disease. FAD PReP Foreign Animal Disease Preparedness & Response Plan. NAHEMS National Animal Health Emergency Management System. USDA and The Center for Food Security & Public Health. Iowa State University U. May

2015. **http://www.cfsph.iastate.edu/pdf/fad-prep-nahems-appendix-a-vaccination-for-foot-and-mouth-disease**.

3. The Center for Food Security & Public Health. Iowa State University, USA. **http://www.cfsph.iastate.edu/Factsheets/pdfs/foot_and_mouth_disease.pdf**
World Organization for Animal Health: OIE Terrestrial Manual. Manual of Diagnostic tests and vaccines for terrerstrial animals 2015. Accessed on line. **http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/**.

ANNEX 1: Epidemiological patterns FMD in Africa

Summarised from: Maree et al, 2014. Challenges and prospects for the control of FMD: an African perspective [7].

In Africa, the FMDV serotypes are not uniformly distributed, and each serotype results in different epidemiological patterns. The cumulative incidence of FMDV serotypes show that six of the seven serotypes of FMD (O, A, C, SAT1, SAT2, and SAT3) have occurred in Africa. The distribution of five serotypes and the different topotypes are shown in Figures in next page, A-E. Based on the genetic characterization of the virus and antigenic relationship of FMDV in Africa, the virus distribution has been divided into three virus pools: namely, pool 4 covering East and North Africa, with predominance of serotypes A, O, SAT1, and SAT2; pool 5 restricted to West and northern Africa, with serotypes O, A, SAT1, and SAT2; and pool 6 restricted mainly to South Africa, with SAT1, SAT2, and SAT3 serotypes (Figure 2 of the document).

To understand the complexity of FMD epidemiology in Africa and to assist decision making and improve the continental control of FMD, it is important to further divide the virus pools into epidemiological clusters. Rweyemamu et al proposed eight epidemiological clusters for Africa (Figure F) based on the distribution of serotypes and topotypes in different regions in Africa, animal movement patterns, impact of wildlife, and farming systems. The epidemiological clusters for Africa have the following characteristics:

1. Indian Ocean Island Countries (Madagascar, Mauritius, and Seychelles) are free of FMD, with a recognized status of FMD freedom without vaccination.

2. The South Southern African Development Community (SADC) cluster includes Swaziland, Lesotho, South Africa, Botswana, and Namibia, the southern and western part of Zimbabwe, and the southern part of Mozambique. The commercial livestock sectors of South SADC countries, with the exception of Zimbabwe and Mozambique, are free from FMD and meet the conditions of the OIE for zonal or country freedom from FMD without vaccination. Over the last 5 years, the region has suffered from an increasing number of outbreaks in cattle, most of which has been caused by SAT2 viruses. The epidemiology of FMD in this region is characterized by virus circulation between the African buffalo, and domestic animals, as well as spread among domestic animals, without the involvement of wildlife. In some of these countries, there are segregated wildlife areas that harbor African buffalo known to be infected, asymptomatically, with FMDV serotypes SAT1, SAT2, and SAT3.

3. The North SADC cluster comprises the northern part of Zimbabwe, Zambia, northern Mozambique, Malawi, and southern Tanzania. The North SADC cluster countries have to deal with at least four serotypes of the virus (A, O, SAT1, and SAT2), and maybe even five (SAT3), each with multiple subtypes in the region. Cross-border spread of the disease is common, and SAT1 and/or SAT2 outbreaks in Mozambique, Malawi, and Zambia between 2002 and 2013 were either because of outbreaks spreading from neighboring countries or to internal buffalo–cattle contact. Northern Malawi and Northern Zambia are under constant threat of FMD spread from southern Tanzania.

4. The Angola cluster may also include the western Democratic Republic of Congo (DRC). Very little is known about the true incidence of FMD within this cluster, and no official information is available on the isolation of FMDV from Angola since 1974. However, an FMD outbreak has been recorded in Angola in 2009, although no virus could be isolated. The southern part of Angola forms part of the Kavango-Zambezi TFCA, and it may be appropriate to include it within the South SADC cluster.

5. The East African Community (EAC) cluster is comprised of Tanzania, Uganda, Kenya, Rwanda, and Burundi, plus the eastern part of the DRC. In addition to large livestock populations, this cluster has the highest concentration of wildlife in the world. The transmission and maintenance of FMD in this region is complex, as farming practices, trade, and wildlife contribute to the maintenance and spread of the virus. Farming is dominated by agro-pastoral and pastoral communities and is characterized by communal grazing and migrations. Eastern DRC is heavily dependent on trade in livestock from Uganda, Tanzania, Rwanda, and Burundi. The cluster probably contains several FMD primary endemic foci, and cross-border epidemiological events suggest that animal movement plays an important role in virus dissemination. At least four serotypes (A, O, SAT1, and SAT2) are endemic in this cluster, with serological evidence for a fifth serotype (C). A sixth serotype (SAT3) was isolated in wildlife (African buffalo) in Uganda in 1970, although it has never been isolated from livestock in this cluster. SAT3 was also reported in Uganda in 1997 and in the DRC in 2005, but was not genotyped. The role of the African buffalo in the maintenance and transmission of FMD serotypes (eg, A and O) that occur in this cluster has not been systematically studied.

6. The Intergovernmental Authority on Development (IGAD) cluster comprises Sudan, South Sudan, Eritrea, Ethiopia, Djibouti, Somalia, Northern Kenya, and Northern Uganda. Similar to the EAC cluster, this cluster probably harbors major FMD primary endemic foci. Historically, isolates of serotypes A, O, SAT1, and SAT2 from Sudan and Ethiopia were genetically related to isolates from Uganda, Kenya, and Tanzania, most likely as a result of cross-border movement, a situation that has not changed.

7. The Soudan/Sahel cluster comprises Western Sudan, Niger, Chad, Burkina Faso, Mali, Northern Nigeria, Senegal, and Mauritania. The farming system in this ecosystem is predominantly pastoral, characterized by long-distance movement of livestock due to either transhumance or trade. This cluster probably also contains important FMD primary endemic areas, and at least four serotypes (A, O, SAT1, and SAT2) of the virus have been found. Furthermore, it may be an important disease-corridor cluster, linking the IGAD cluster with West Africa and probably West Africa with North Africa. Although the epidemiology of FMD in the coastal belt countries of West and Central Africa has not been deeply studied, it seems that this cluster probably gets infected from the Soudan/Sahel cluster. It could therefore be described as secondary endemic.

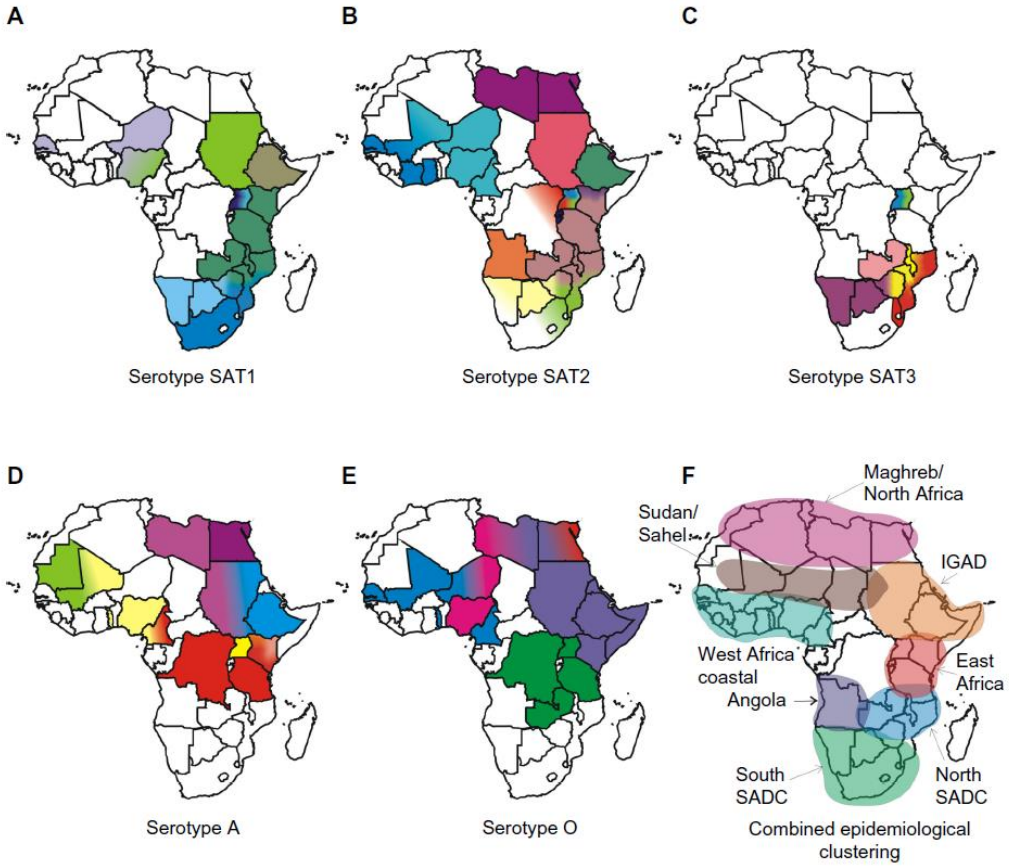
8. North Africa/Maghreb cluster countries Morocco, Algeria, and Tunisia have not reported FMD since 1999, most likely because of routine preventive vaccination and other measures. Libya and Egypt have sporadic FMD, and take routine preventive vaccination. Libya reported a SAT2 outbreak in 2003, probably as a result of live animal introductions from neighboring countries to the south, breaching the Sahara barrier. Libya experienced another SAT2 outbreak, this time genetically related to isolates from Sudan (2007) and Nigeria

(2008). Egypt also reported a SAT2 outbreak in 2012, the first occurrence of this serotype since 1950. Egypt also reported African type A viruses in 2006, 2007, 2009, and 2012, as well as ME-SA (Middle East–South Asia) types O and A. Yemen reported EA (East Africa)-3 type O in 2007 and 2009. Thus, North African countries will remain at risk from the south and east, but across the majority of their territories, and at-risk populations should effectively maintain FMD freedom.

Maps of Africa showing the serotypes and topotype distribution.

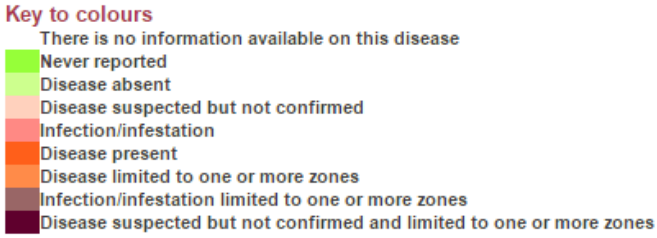
Notes: The topotypes are color coded. The epidemiological clustering is indicated. The epidemiological clusters shown A-F do not necessarily indicate the borders of the countries.

Source: Maree et al, 2014 [7]



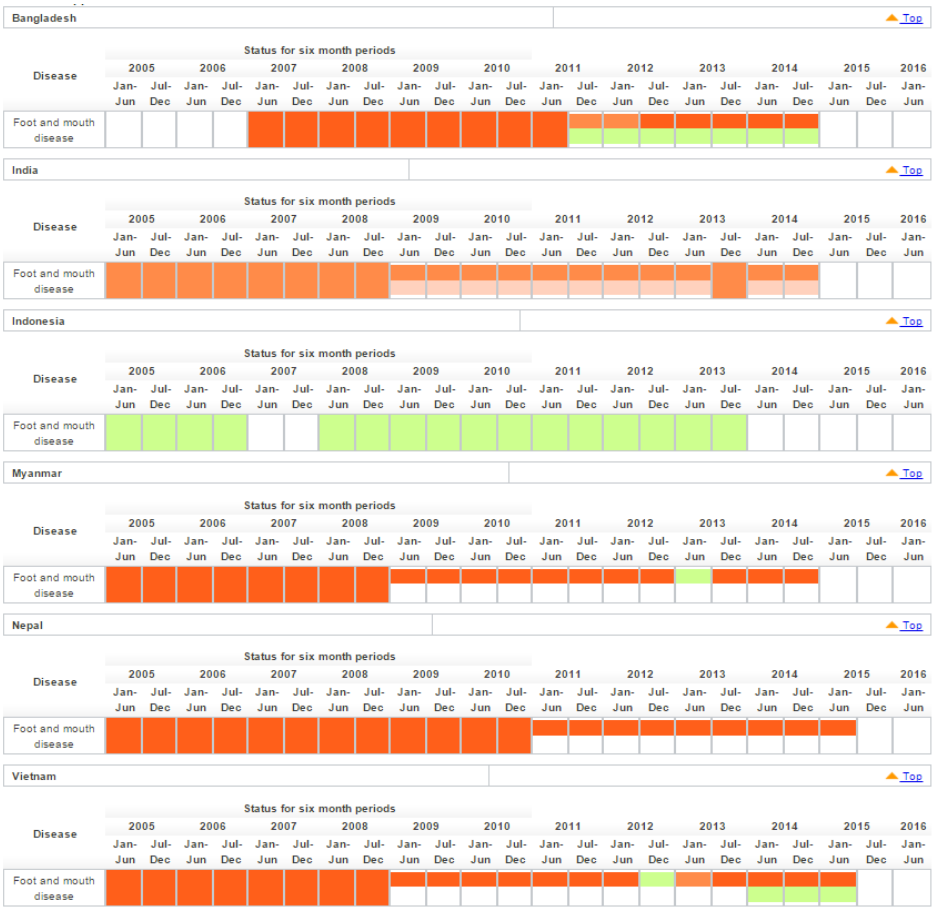
ANNEX 2: Additional data on disease presence and incidence

Reports to OIE on FMD:



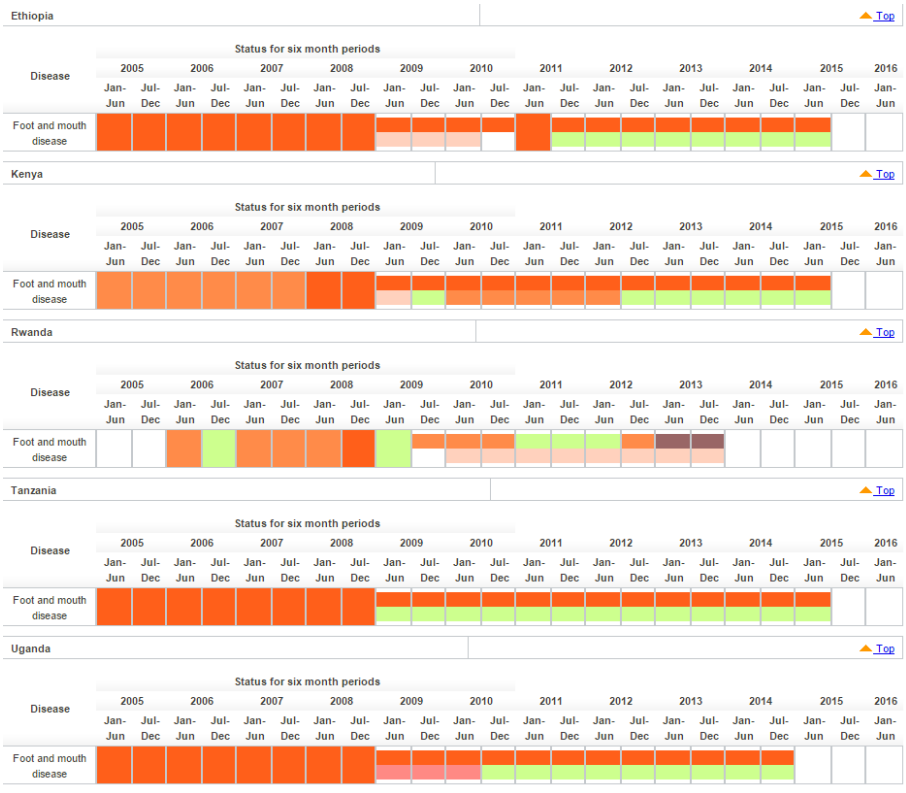
When different animal health statuses between domestic and wild animal population are provided, the box is split in two: the upper part for domestic animals, and the lower part for wild animals.

FMD in Asia: Bangladesh, India, Indonesia, Myanmar, Nepal and Vietnam

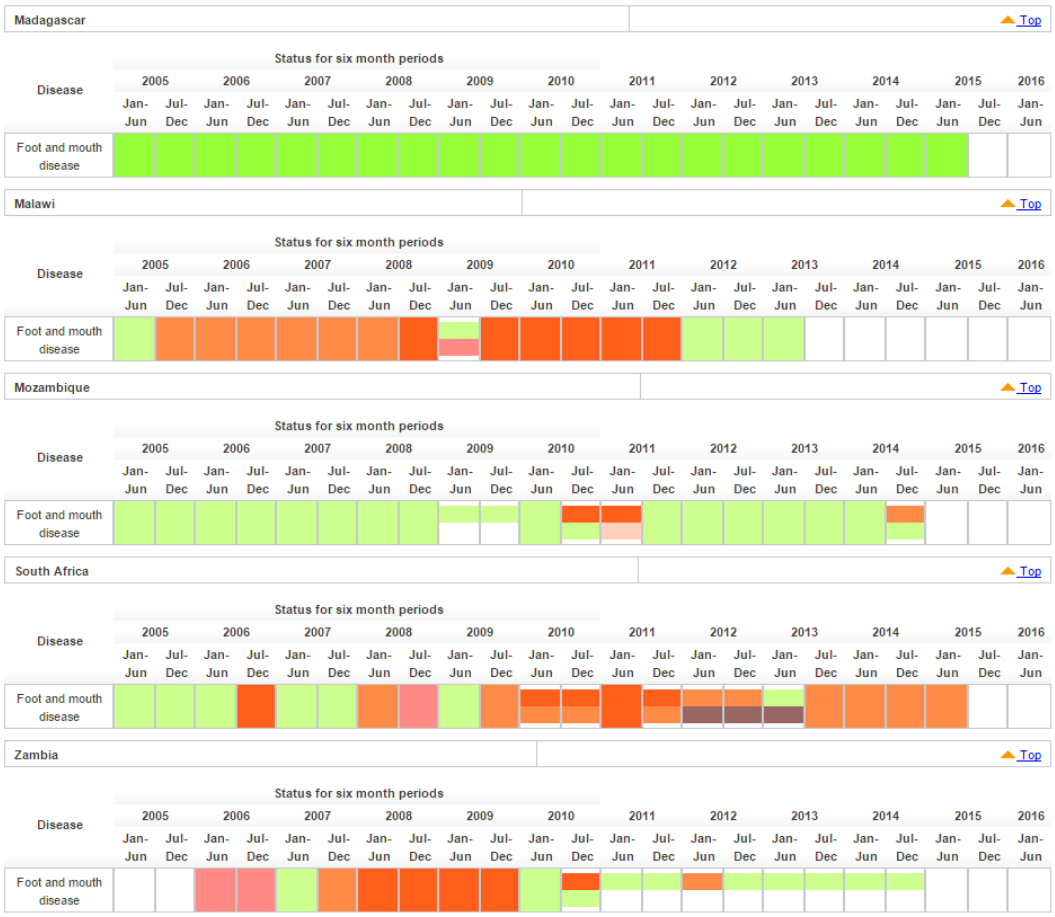


FMD in Western Africa: Burkina Faso, Ivory Coast, Mali and Senegal

FMD in Eastern Africa: Ethiopia, Kenya, Rwanda, Tanzania and Uganda



FMD in Southern Africa: Madagascar, Malawi, Mozambique, South Africa and Zambia



ANNEX 3: Cost benefit analysis studies of FMD control and eradication programs

Source: Knight-Jones & Rushton, 2013. The economic impacts of FMD – what are they, how big are they and where do they occur? *Preventive Veterinary Medicine* 112 (2013) 161-173.

Country	Export potential	Returns to control	Analysis	Author
Australia	Large	A 6 month outbreak would reduce GDP by 0.6%	Simulation	Garner et al. (2002)
Australia	Large	Losses to the national economy of $2–3 billion or $8–13 billion can be expected depending on outbreak length	Simulation	Productivity Commission (2002)
Bhutan	Nil	Positive when control focused on endemic areas, negative if unfocussed	Data analysis	Tshering (1995)
Bolivia	Small	Negative, analysis was based on a prolonged programme and reliable data	Data analysis	FAO (1995)
Bolivia	Small	Positive, but with a short intensive vaccination campaign in the endemic areas	Data analysis	PANAFTOSA (1997)
Bolivia	Small	Positive, but control of FMD is not economic for extensive systems, hence greater public funding is required	Data analysis	Rushton (2008)
Botswana	Large	Positive with exports, negative without exports	Data analysis	Oarabile (1994)
Canada	Large	Even a small outbreak could cost $2 billion over 5 years	Simulation	Krystynak and Charlebois (1987)
France	Large	Rapidly regaining export market access is key, this is best achieved by stamping out	Simulation	Mahul and Durand (2000)
UK	At that time small	Positive for both a stamping out policy and for vaccination	Data analysis	Power and Harris (1973)
India	Small	Positive due to the large returns in the milk sector	Data analysis	Ellis and James (1976)
Netherlands	Large	Culling is preferable in areas of low livestock density, vaccination is preferable in areas of high density. Market acceptance of products from FMD vaccinated animals reduces the impact of an outbreak	Simulation	Backer et al. (2009)
Netherlands	Large	The 2001 FMD outbreak cost the nation €1billion	Data analysis	Huirne et al. (2002)
New Zealand	Large	An outbreak could cost $NZ10 billion, with eradication by slaughter being preferable to vaccinate to live	Simulation	Belton (2004)
Philippines	Unknown	Positive, particularly benefiting the commercial pig sector. Benefit-cost ratio of 1.6–12 depending on level of exports	Data analysis	Randolph et al. (2002)
Sudan	Nil	Positive with increased food security. Benefit-cost ratio of 11.5 with successful vaccination	Data analysis	Barasa et al. (2008)
Southern Cone	Large	Positive for both culling and vaccination strategies, does not deal with social impacts and feasibility of implementation	Data analysis + simulation	Rich and Winter-Nelson (2007)
Taiwan	Large (pig products to Japan)	Returns according to the information on eradication are large with costs of eradicating the 1997 outbreak estimated to be US$378.9 million, but with potential export losses of approx. US$1.2 billion	Data analysis	Yang et al. (1999)
Taiwan	Large	Losses due to the 1997 FMD outbreak were experienced in many sectors, causing a 0.28% loss to GDP	Data analysis	Hsu et al. (2005)
Thailand	Possible	Positive with a benefit cost ratio of 3.73 and 15 with and without export of livestock products respectively	Data analysis	Perry et al. (1999)
Turkey	Unknown	Culling certain highly susceptible cattle could be viable	Data analysis	Şentürk et al. (2008)
UK	Large	The lowest cost strategy comparing vaccination to culling depended on other factors, such as outbreak size	Simulation	Risk_Solutions (2005)
UK	Large	Vaccination may not be the most effective way of controlling an outbreak, however, speed of regaining export market access is not the only consideration	Data analysis	Rushton et al. (2002)
UK	Large	GDP fell by less than 0.2% due to the 2001 FMD outbreak	Data analysis	Thompson et al. (2002)
USA	Large	Vaccination based eradication provides the best return when the vaccine is effective	Simulation	Bates et al. (2003)
USA	Large	If time to outbreak detection extends beyond 21 days, every additional hour delay results in extra losses in the order of $565 million	Simulation	Carpenter et al. (2011)
USA	Large	A large FMD outbreak could lead to a $14 billion loss in farm income, with loss of exports and fall in demand due to consumer fears	Data analysis	Paarlberg et al. (2002)
Uruguay	Strong	Control brings strong positive returns based on the access to export markets (20,000 tonnes beef export to USA)	Data analysis	Leslie et al. (1997)
Southern Africa	Strong at that time	Positive benefit, particularly for commercial farms, less so for the poor. Every dollar saved on control leads to $5 lost to the economy	Data analysis	Perry et al. (2003) and Randolph et al. (2005)